



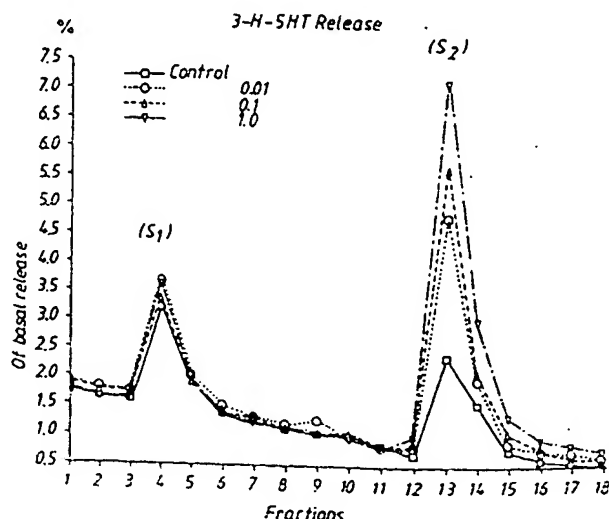
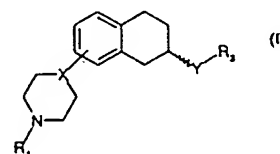
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(21) International Application Number: PCT/SE97/00469 (22) International Filing Date: 20 March 1997 (20.03.97) (30) Priority Data: 9601110-1 22 March 1996 (22.03.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BERG, Stefan [SE/SE]; Gräsåkersvägen 39 D, S-178 36 Ekerö (SE). FLORVALL, Lennart [SE/SE]; Snickarstigen 7, S-151 62 Södertälje (SE). ROSS, Svante [SE/SE]; Hedvägen 8, S-151 52 Södertälje (SE). THORBERG, Seth-Olov [SE/SE]; Kalkbro Gård, S- 645 91 Strängnäs (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: SUBSTITUTED 1,2,3,4-TETRAHYDRONAPHTHALENE DERIVATIVES

(57) Abstract

New piperidinyl- or piperazinyl-substituted-1,2,3,4-tetrahydronaphthalene derivatives having formula (I) wherein X is N or CH; Y is NR₂CH₂, CH₂-NR₂, NR₂-CO, CO-NR₂ or NR₂SO₂; R₁ is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl; R₃ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl or (CH₂)_n-aryl, where aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted; n is 0-4; as (R)-enantiomer, (S)-enantiomer or a racemate in the form of the free base or a pharmaceutically acceptable salt or hydrate thereof; a pharmaceutical formulation containing the compounds, use of the compounds in the treatment of 5-hydroxytryptamine mediated disorders, processes for the preparation of the compounds and intermediates for the preparation of the compounds.



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SUBSTITUTED 1,2,3,4-TETRAHYDRONAPHTHALENE DERIVATIVES

Field of the Invention

The present invention relates to the new compounds, piperidinyl- or piperazinyl-substituted-
5 1,2,3,4-tetrahydronaphthalene derivatives as (R)- enantiomers, (S)-enantiomers or
racemates in the form of a free base or pharmaceutically acceptable salts thereof, a process
for their preparation, pharmaceutical compositions containing said therapeutically active
compounds and to the use of said active compounds in therapy.

10 An object of the invention is to provide compounds for therapeutic use, especially
compounds having a selective effect at a subgroup of 5-hydroxy-tryptamine receptors,
designated the 5-HT_{1D}-receptor in mammals including man.

It is also an object of the invention to provide compounds with a therapeutic effect after
15 oral administration.

Prior Art

Different classes of piperazinyl substituted benzanilide derivatives as 5-HT_{1D} antagonists
are disclosed in inter alia EP 533266, EP 533267, EP 533268, GB 2273930 and
20 WO 95/11243 .

WO 94/13659 discloses an extremely broad class of fused benzo compounds having a para
substituted piperidinyl or piperazinyl radical in the aromatic ring, said class of compounds
are stated to bind to the 5-HT_{1A} receptor.

25 WO 94/21619 discloses fully aromatic naphthalene ring system which may be substituted
with a piperidinyl or piperazinyl group, said compounds are also stated to be potent
serotonin (5HT₁) agonists and antagonists.

EP 402923 discloses 2-aminoalkyl or alkylaromatic substituted 1,2,3,4-tetrahydronaphthalene derivatives having a further nitrogen substitution in the 5 position in the tetraline ring, said compounds act as dopamine agonists.

5 **Background of the Invention**

Various central nervous system disorders such as depression, anxiety, etc. appear to involve the disturbance of the neurotransmitters noradrenaline (NA) and 5-hydroxytryptamine (5-HT), the latter also known as serotonin. The drugs most frequently used in the treatment of depression are believed to act by improving the neurotransmission of either or both of these physiological agonists. It appears that the enhancement of 5-HT neurotransmission primarily affects the depressed mood and anxiety, whereas the enhancement of noradrenaline neurotransmission affects the retardation symptoms occurring in depressed patients. The invention concerns compounds which have an effect on 5-HT neurotransmission.

15 Serotonin, or 5-HT, activity is thought to be involved in many different types of psychiatric disorders. For instance it is thought that an increase in 5-HT activity is associated with anxiety, while a decrease in 5-HT release has been associated with depression. Serotonin has in addition been implicated in such diverse conditions as eating disorders, gastrointestinal disorders, cardiovascular regulation and sexual behavior.

20 **The 5-HT Receptors**

The various effects of 5-HT may be related to the fact that serotonergic neurons stimulate the secretion of several hormones, e.g. cortisol, prolactin, β -endorphin, vasopressin and others. The secretion of each of these other hormones appears to be regulated on a specific basis by several different 5-HT (serotonin) receptor subtypes. With the aid of molecular biology techniques, to date these receptors have been classified as 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇ with the 5-HT₁ receptor further divided into the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F} subtypes. Each receptor subtype is involved in a different serotonin function and has different properties.

Regulation of the 5-HT transmission

The release of 5-HT at the nerve terminals is feedback-regulated by two different subtypes of 5-HT receptors. Inhibitory 5-HT_{1A} autoreceptors are located on the cell bodies in the raphé nuclei which upon stimulation by 5-HT decrease the impulse propagation in the 5-HT neurons and thereby reduce the 5-HT release at the nerve terminals. Another subtype of inhibitory 5-HT receptors is located on the 5-HT nerve terminals, the 5-HT_{1D} receptors (in rodents the 5-HT_{1B} receptors) which regulate the synaptic concentration of 5-HT by controlling the amount of 5-HT that is released. An antagonist of these terminal autoreceptors thus increases the amount of 5-HT released by nerve impulses, as has been shown in both *in vitro* and *in vivo* experiments.

The use of an antagonist of the terminal 5-HT_{1D} autoreceptor will accordingly increase the synaptic 5-HT concentration and enhance the transmission in the 5-HT system. The antagonist would thus produce an antidepressant effect making it useful as a medication for depression.

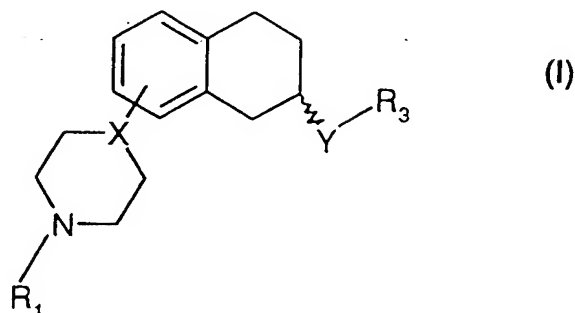
Other localizations of 5-HT_{1D} receptor subtype also exist. A large part of these receptors appear to be located on nerve terminals of other neuronal systems (so called heteroreceptors). Since the 5-HT_{1D} receptor mediates inhibitory responses, an antagonist of this receptor subtype might also increase the release of other neurotransmitters than 5-HT.

Compounds having 5-HT_{1D} activity may according to well known and recognized pharmacological tests be divided into full agonists, partial agonists and antagonists.

Disclosure of the Invention

The primary object of the present invention is to provide compounds having a selective effect at the 5-HT_{1D} receptor, preferably antagonistic properties, as well as having a good bioavailability. The effect on the other receptors chosen from, for example, the 5-HT_{1A}, 5-HT_{2A}, D₁, D_{2A}, D₃, α_1 and α_2 receptor has been investigated.

Accordingly, the present invention provides compounds of the formula I



5 wherein

X is N or CH ;

Y is NR₂CH₂, CH₂-NR₂, NR₂-CO, CO-NR₂ or NR₂SO₂ ;

R₁ is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl ;

R₂ is H or C₁-C₆ alkyl ;

10 R₃ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl or (CH₂)_n-aryl,

where aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted with R₄ and/or R₅;

R₄ is H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, halogen, CN, CF₃, OH, C₁-C₆ alkoxy, NR₆R₇,

OCF₃, SO₃CH₃, SO₃CF₃, SO₂NR₆R₇, phenyl, phenyl-C₁-C₆ alkyl, phenoxy, C₁-C₆ alkyl

15 phenyl, C₁-C₆ alkyl-heterocyclic ring containing one or two heteroatoms or substituted heteroatoms selected from N, O, S, SO and SO₂, an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms or substituted heteroatoms selected from N, O, S, SO and SO₂, wherein the optionally substituent(s) is(are) selected from C₁-C₆ alkyl, C₃-C₆ cycloalkyl and phenyl-C₁-C₆ alkyl; or COR₈;

20 R₅ is H, OH, CF₃, OCF₃, halogen, C₁-C₆ alkyl or C₁-C₆ alkoxy;

R₆ is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

R₇ is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

R₈ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, CF₃, NR₆R₇, phenyl, or a heterocyclic ring containing one or two heteroatoms or substituted heteroatoms selected from N, O, S, SO and SO₂;

25 n is 0-4;

as (R)-enantiomer, (S)-enantiomer or a racemate in the form of the free base or a pharmaceutically acceptable salt or hydrate thereof which possess a high selective effect at the 5-HT_{1D} receptor and also shows sufficient bioavailability after oral administration.

5 In the present context C₁-C₆ alkyl may be straight or branched. C₁-C₆ alkyl may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl.

In the present context C₁-C₆ alkoxy may be straight or branched. C₁-C₆ alkoxy may be
10 methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, i-pentyloxy, t-pentyloxy, neo-pentyloxy, n-hexyloxy or i-hexyloxy.

In the present context C₃-C₆ cycloalkyl may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably cyclohexyl.

15

In the present context halogen may be fluoro, chloro, bromo or iodo.

In the present context the heteroaromatic ring containing one or two heteroatoms selected from N, O and S preferably is a 5- or 6-membered heteroaromatic ring and may be furyl,
20 imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl or thienyl. The heteroaromatic ring can be either substituted or unsubstituted.

In the present context the heterocyclic ring containing one or two heteroatoms or
25 substituted heteroatoms selected from N, O, S, SO and SO₂ may optionally contain a carbonyl function and is preferably a 5-, 6- or 7-membered heterocyclic ring and may be imidazolidinyl, imidazoliny, morpholinyl, piperazinyl, piperidinyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, thiomorpholinyl, preferably piperidino, 1-piperazinyl, morpholino, thiomorpholino and 4-piperidon-1-yl.

A preferred embodiment of the invention relates to compounds of formula I wherein the piperidinyl or piperazinyl is in the 5 position. The most preferred embodiment of the invention relates to compounds of formula I wherein the piperidinyl or piperazinyl is in the 8 position. Another possibility is that the piperidinyl or piperazinyl is in the 6 or 7 position.

5

Another preferred embodiment of the invention relates to compounds of formula I wherein Y is NHCO or CONH i.e. amides. Of those compounds, the compounds wherein R₃ is unsubstituted phenyl, or mono- or di- substituted phenyl, and especially ortho-, meta- or para- substituted phenyl, and particularly those wherein the substituent R₄ is phenyl, phenyl-
10 C₁-C₆ alkyl, cyclohexyl, piperidino, 1-piperazinyl, morpholino, CF₃, 4-piperidon-1-yl, n-butoxy or COR₈ wherein R₈ is phenyl, cyclohexyl, 4-piperidon-1-yl, 1-piperazinyl, morpholino, CF₃, piperidino or NR₆R₇, are preferred.

Examples of suitable combinations of substituents are:

15

X is N, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is piperidinyl, R₅ is H;

X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

20 X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl, R₄ is piperidinyl, R₅ is H;

X is CH, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

X is CH, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl, R₄ is
25 piperidinyl, R₅ is H;

X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl;

X is CH, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl;

X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

30

X is CH, Y is NR_2CO , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is phenyl, R_4 is morpholinyl, R_5 is H;

X is CH, Y is CONR_2 , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is phenyl, R_4 is morpholinyl, R_5 is H;

5 X is CH, Y is CONR_2 , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is phenyl, R_4 is piperidinyl, R_5 is H;

X is N, Y is CONR_2 , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is CH_2 -phenyl, R_4 is morpholinyl, R_5 is H;

10 X is N, Y is NR_2CO , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is CH_2 -phenyl, R_4 is morpholinyl, R_5 is H;

X is CH, Y is NR_2CO , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is $(\text{CH}_2)_2$ -phenyl, R_4 is piperidinyl, R_5 is H;

X is CH, Y is CONR_2 , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is phenyl;

15 X is N, Y is CONR_2 , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is phenyl, R_4 is morpholinyl, R_5 is H;

X is N, Y is CONR_2 , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is phenyl, R_4 is piperidinyl, R_5 is H;

X is CH, Y is NR_2CO , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is (CH_2) -phenyl;

20 X is CH, Y is NR_2CO , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H;

X is N, Y is CONR_2 , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is $(\text{CH}_2)_2$ -phenyl;

X is N, Y is CONR_2 , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is CH_2 -phenyl, R_4 is piperidinyl, R_5 is H;

25 X is N, Y is NR_2CO , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is $(\text{CH}_2)_2$ -phenyl, R_4 is piperidinyl, R_5 is H;

X is N, Y is CONR_2 , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H;

X is N, Y is NR_2CO , R_1 is H, CH_3 , C_2H_5 or C_3H_7 , R_2 is H, R_3 is phenyl, R_4 is morpholinyl, R_5 is H;

X is CH, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is piperidinyl, R₅ is H;

X is N, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl;

X is N, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is morpholinyl, R₅ is H;

X is N, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl, R₄ is COR₈, R₈ is morpholinyl;

X is CH, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

X is CH, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is morpholinyl, R₅ is H;

X is N, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

X is CH, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is piperidinyl, R₅ is H;

X is CH, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is COR₈, R₈ is NR₆R₇, R₆R₇CH₃, C₂H₅ or C₃H₇;

X is CH, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

X is CH, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is morpholinyl, R₅ is H;

X is CH, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl;

X is CH, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

X is CH, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is morpholinyl, R₅ is H;

X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl, R₄ is COR₈, R₈ is morpholinyl;

X is CH, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl;

X is CH, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

X is CH, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is morpholinyl, R₅ is H;

X is CH, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl;

X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl;

X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is piperidinyl, R₅ is H;

X is N, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl, R₄ is phenyl, phenylmethyl or phenylethyl, R₅ is H;

X is CH, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is piperidinyl, R₅ is H;

X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is (CH₂)₂-phenyl, R₄ is morpholinyl, R₅ is H;

X is N, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl, R₄ is COR₈, R₈ is cyclohexyl;

X is N, Y is CONR₂, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is phenyl;

X is N, Y is NR₂CO, R₁ is H, CH₃, C₂H₅ or C₃H₇, R₂ is H, R₃ is CH₂-phenyl.

Preferred compounds are:

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-

(trifluoroacetyl)benzamide,

(*R*)-*N*-[8-(1-Methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-piperidinobenzamide,

(*S*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-*N,N*-diethylaminobenzamide,

(*R*)-*N*-[8-(4-Propylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-ethylbenzamide,

- (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinocarbonylbenzamide,
- (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,
- (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-butoxybenzamide,
- 5 (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(1H-pyrrol-1-yl)benzamide,
- (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-methyl-4-morpholinobenzamide,
- (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-ethylphenyl)benzamide,
- 10 (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylbenzamide,
- (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(*N,N*-dipropylaminosulphonyl)benzamide,
- 15 (*R*)-*N*-[8-(4-Ethylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,
- (*R*)-*N*-[8-(1-Methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylbenzamide,
- (*R*)-*N*-[8-(1-Methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-butoxybenzamide,
- (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-cyclohexylbenzamide,
- 20 (*R*)-*N*-[8-(Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-piperidon-1-yl)benzamide,
- (*R*)-*N*-8-(Piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,
- N*-(4-Morpholinocarbonylphenyl)-8-[4-(methylpiperazin-1-yl)]-1,2,3,4-tetrahydronaphthalene-2-carboxamide,
- 25 (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-morpholinomethyl)benzamide,
- (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(*N,N*-dimethylaminocarbonyl)benzamide,
- (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-
- 30 morpholinocarbonylbenzamide or

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-thiomorpholinobenzamide

Another preferred group of compounds are:

5 (R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-2-methylbenzamide

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-cyanobenzamide

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-fluorobenzamide

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-

10 hydroxyphenyl)benzamide

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-phenoxybenzamide

The compounds of the present invention are in the form of the racemate or the (R)- or (S)-
15 enantiomer in the form of a free base or a pharmaceutically acceptable salt or hydrate thereof. Compounds in the form of the (R)-enantiomer are preferred ones.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. Illustrative acids are
20 sulfuric, nitric, phosphoric, oxalic, hydrochloric, formic, hydrobromic, citric, acetic, lactic, tartaric, dibenzoyltartaric, diacetyltartaric, palmoic, ethanedisulfonic, sulfamic, succinic, propionic, glycollic, malic, gluconic, pyruvic, phenylacetic, 4-aminobenzoic, anthranilic, salicylic, 4-aminosalicylic, 4-hydroxybenzoic, 3,4-dihydroxybenzoic, 3,5-dihydroxybenzoic, 3-hydroxy-2-naphthoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic,
25 benzenesulfonic, p-toluenesulfonic, sulfanilic, naphthalenesulfonic, ascorbic, cyclohexylsulfamic, fumaric, maleic and benzoic acids. These salts are readily prepared by methods known in the art.

Pharmaceutical Formulations

In a second aspect the present invention provides a pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I as an enantiomer or a racemate in the form of a free base or a pharmaceutically acceptable salt or hydrate thereof, optionally in association with diluents, excipients or inert carriers.

According to the present invention the compound of the invention will normally be administered orally, rectally or by injection, in the form of pharmaceutical formulations comprising the active ingredient either as a free base or a pharmaceutically acceptable non-toxic acid addition salt, e.g. the hydrochloride, hydrobromide, lactate, acetate, phosphate, sulfate, sulfamate, citrate, tartrate, oxalate and the like in a pharmaceutically acceptable dosage form. The dosage form may be a solid, semisolid or liquid preparation. Usually the active substance will constitute between 0.1 and 99% by weight of the preparation, more specifically between 0.5 and 20% by weight for preparations intended for injection and between 0.2 and 50% by weight for preparations suitable for oral administration.

To produce pharmaceutical formulations containing the compound of the invention in the form of dosage units for oral application, the selected compound may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatin or polyvinylpyrrolidone, or a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer known to the person skilled in the art, dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish among tablets containing different active substances or different amounts of the active compound.

For the preparation of soft gelatin capsules, the active substance may be admixed with e.g. a vegetable oil or poly-ethylene glycol. Hard gelatin capsules may contain granules of the active substance using either the above mentioned excipients for tablets e.g. lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin),
5 cellulose derivatives or gelatin. Also liquid or semisolid forms of the drug can be filled into hard gelatin capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substance in a mixture with a neutral fatty base,
10 or in the form of gelatin rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil. Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing from about 0.1% to about 20% by weight of the active substance herein described, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may con-
15 tain colouring agents, flavouring agents, saccharine and carboxymethyl-cellulose as thickening agent or other excipients known to the person skilled in the art.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance, preferably in a
20 concentration of from about 0.1% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable daily doses of the compound of the invention in therapeutical treatment of humans
25 are about 0.01-100 mg/kg bodyweight for peroral administration and 0.001-100 mg/kg bodyweight for parenteral administration.

Medical and Pharmaceutical Use

In a further aspect the present invention provides the use of the compounds of formula I in
30 therapy as 5-HT_{1D} antagonists, partial agonists or full agonists, preferably as antagonists

and the use in the treatment of 5-hydroxytryptamine mediated disorders. Examples of such disorders are disorders in the CNS such as mood disorders (depression, major depressive episodes, dysthymia, seasonal affective disorder, depressive phases of bipolar disorder), anxiety disorders (obsessive compulsive disorder, panic disorder with/without agoraphobia, social phobia, specific phobia, generalized anxiety disorder, posttraumatic stress disorder), personality disorders (disorders of impulse control, trichotellomania), obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders (age associated memory impairment, presenile and senile dementia), pathological aggression, schizophrenia, endocrine disorders (e g hyperprolactinaemia), stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders, pain and hypertension. Other examples of 5-hydroxytryptamine mediated disorders are urinary incontinence, vasospasm and growth control of tumors (e g lung carcinoma).

Methods of Preparation

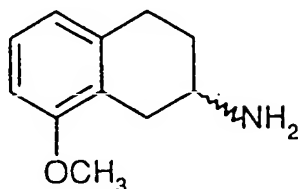
The present invention also relates to processes for preparing the compounds of formula (I). Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis" T.W. Greene, Wiley-Interscience, New York, 1991.

The below described methods for substitution in the 8-position are also applicable to substitution in the 5-position.

Methods of Preparation of Intermediates

I.

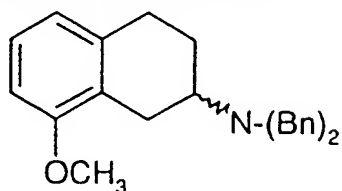
(i) Benzylation of the compound of the formula (II), either as a racemate or as an enantiomer,



(II)

to obtain a compound of formula (III) may be carried out by reaction with a suitable benzylation agent e.g. a benzyl halide such as benzyl bromide or benzyl chloride or an activated alcohol e.g. benzylmesylate or benzyltosylate. The reaction may be carried out using a salt or the base of compound (II) in a suitable solvent e.g. *N,N*-dimethylformamide, acetone or acetonitrile with a suitable base e.g. NaOH, NaHCO₃, K₂CO₃ or a trialkylamine such as triethylamine at a temperature within the range of +20 °C to +150 °C. The presence of a suitable catalyst e.g. potassium iodide or sodium iodide, may increase the speed of the reaction. The nitrogen in compound (II) may also be protected by reductive alkylation with an arylaldehyde in the presence of a reductive agent such as sodium cyanoborohydride, sodium borohydride or catalytically with H₂ and a suitable catalyst containing palladium, platinum, rhodium or nickel in a suitable solvent e.g. tetrahydrofuran, dioxane, methanol or ethanol. A proton donor such as *p*-toluenesulfonic acid can be used to catalyze the formation of the imine/enamine, and adjustment of pH to slightly acidic by an appropriate acid such as acetic acid may speed up the reaction, resulting in compound (III).

(ii) Demethylation of the compound of formula (III)



(III)

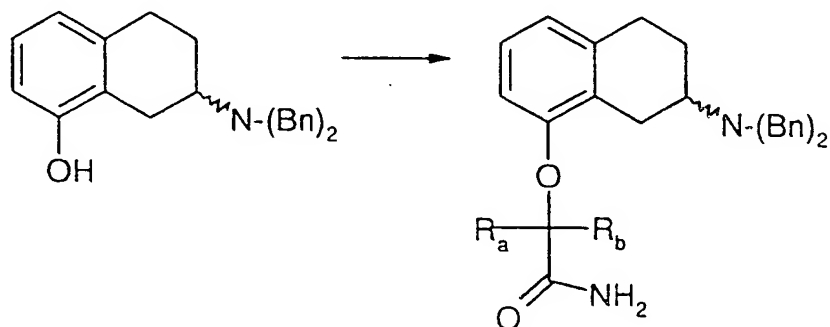
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to obtain a compound of formula (IV) may be carried out by treating the compound with an acidic reagent such as aqueous HBr, HI, HBr/CH₃COOH, BBr₃, AlCl₃, pyridine-HCl or with a basic nucleophilic reagent such as CH₃C₆H₄S⁻ or C₂H₅S⁻ in a suitable solvent.

Suitable solvents may be methylene chloride or chloroform and the reaction may occur

10 between -78 °C and +60 °C.

(iii) Conversion of the compound of formula (IV) to a compound of formula (V)

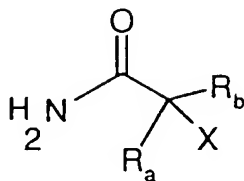


(IV)

(V)

15

may be carried out by the reaction with a compound of formula (VI)

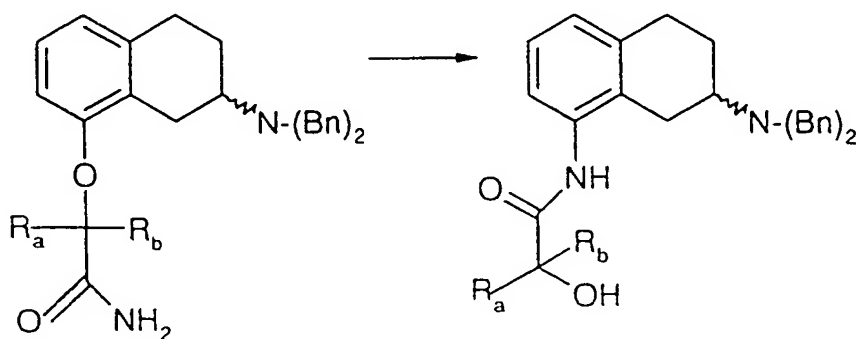


(VI)

- 5 where X stands for a leaving group, e.g. a halogen such as chlorine, bromine or iodine or an alkane- or arenesulfonyloxy group such as a p-toluenesulfonyloxy group and R_a and R_b are hydrogen or a lower alkyl group e.g. methyl. The process may be carried out with a salt of the compound of formula (IV) obtained by reaction with a base such as K_2CO_3 , Na_2CO_3 , KOH , $NaOH$, $BuLi$ or NaH . The reaction may be conducted in a suitable solvent e.g. an
- 10 aprotic solvent such as dioxane, *N,N*-dimethylformamide, tetrahydrofuran, toluene, benzene or petroleum ether and the reaction may occur between +20 °C and +150 °C.

(iv) Rearrangement of a compound of formula (V) to a compound of formula (VII)

15



(V)

(VII)

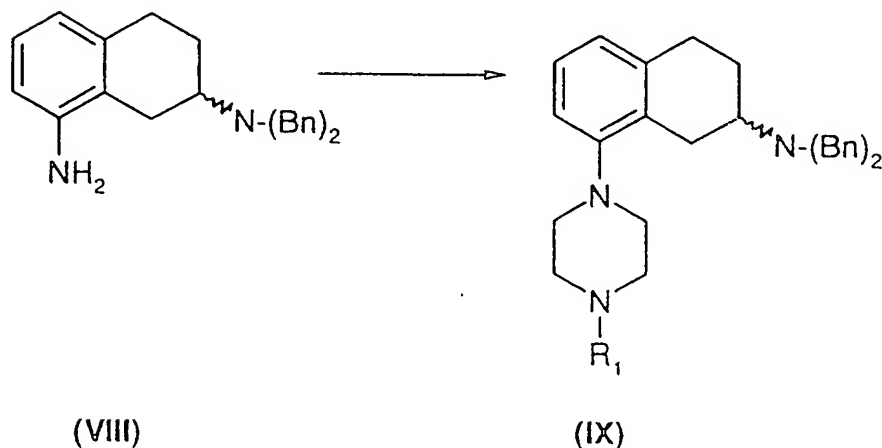
may be carried out in a suitable solvent e.g. aprotic solvent such as *N,N*-dimethylformamide, dioxane, 1,1,3,3-tetramethylurea, tetrahydrofuran or

hexamethylphosphoric triamide with a suitable base e.g. K_2CO_3 , KOH, potassium *tert*-butoxide or NaH at a temperature within the range of +20 °C to +150 °C.

The presence of a cosolvent such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone or hexamethylphosphoric triamide in appropriate concentration in the solvent may increase the speed of the reaction.

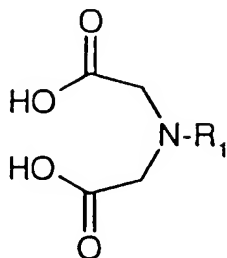
(v) Hydrolysis of a compound of formula (VII) to a compound (VIII) may be carried out under acidic conditions using acids such as H_2SO_4 , HCl or HBr in a suitable solvent e.g. H_2O , ethanol, methanol or mixtures thereof and the reaction may occur between +20 °C and +100 °C or under basic conditions using bases such as NaOH or KOH in a suitable solvent e.g. H_2O , ethanol, methanol or mixtures thereof and the reaction may occur between +20 °C and +100 °C.

(vi) Conversion of compound of formula (VIII) to a compound of formula (IX)



may be carried out by

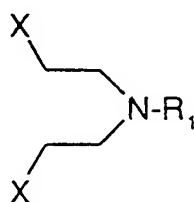
a) reaction with a compound of formula (X)



(X)

- 5 where R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl. The process may be carried out in a suitable solvent e.g. an aprotic/anhydrous solvent such as tetrahydrofuran or *N,N*-dimethylformamide in the presence of coupling reagent such as *N,N'*-carbonyldiimidazole and the reaction may occur between +20 °C and +130 °C. The reaction is followed by the reduction of the imide with a suitable reducing agent e.g. $LiAlH_4$ in a suitable solvent e.g.
- 10 diethyl ether or tetrahydrofuran at a temperature between +20 °C and reflux, or

b) by reaction with a compound of formula (XI)



(XI)

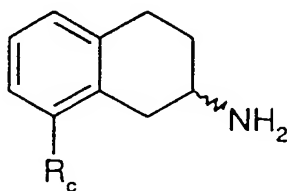
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- where X stands for a leaving group, e.g. a halogen such as chlorine or bromine or an alkane- or arenesulfonyloxy group such as p-toluenesulfonyloxy group and R_1 is C_1 - C_6 -alkyl or C_3 - C_6 cycloalkyl. The process may be carried out in a suitable solvent such as
- 20 ethanol, butanol, *N,N*-dimethylformamide, acetonitrile or a mixture of water and

acetonitrile with a suitable base e.g. K_2CO_3 , $NaHCO_3$ or KOH and the reaction may occur between $+20\text{ }^\circ\text{C}$ and $+150\text{ }^\circ\text{C}$.

Alternatively, a compound of formula (IX) may be prepared by,

(vii) Benzylation of the compound of the formula (XV), either as a racemate or as an enantiomer,

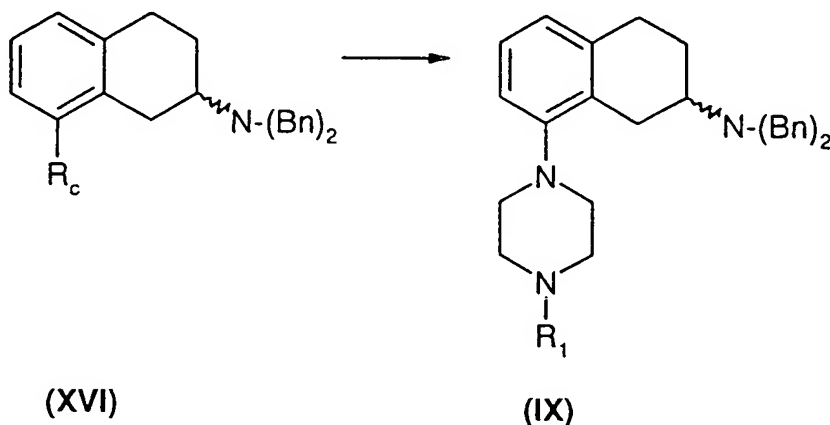


(XV)

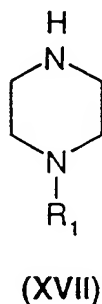
where R_c stands for a halogen such as bromine, iodine or a trifluoromethylsulfonyloxy group, to obtain a compound of formula (XVI) by reaction with a suitable benzylating agent e.g. benzyl halide such as benzyl bromide or benzyl chloride or an activated alcohol e.g. benzylmesylate or benzyltosylate. The reaction may be carried out by using the salt or the base of compound (XV) in a suitable solvent e.g. *N,N*-dimethylformamide, acetone or acetonitrile with a suitable base e.g. $NaOH$, $NaHCO_3$, K_2CO_3 or a trialkylamine such as triethylamine at a temperature within the range of $+20\text{ }^\circ\text{C}$ to $+150\text{ }^\circ\text{C}$. The presence of suitable catalyst e.g. alkali metal iodide such as potassium iodide or sodium iodide may increase the speed of the reaction.

The nitrogen in compound (XV) may also be protected by reductive alkylation with an arylaldehyde in the presence of a reductive agent such as sodium cyanoborohydride, sodium borohydride or catalytically with H_2 and a suitable catalyst containing palladium, platinum, rhodium or nickel in a suitable solvent e.g. tetrahydrofuran, dioxane, methanol or ethanol. A proton donor such as *p*-toluenesulfonic acid can be used to catalyze the

formation of the imine/enamine and adjustment of pH to slightly acidic by an appropriate acid such as acetic acid may speed up the reaction, resulting in compound (XVI).



- (viii) Conversion of the compound of formula (XVI) to a compound of formula (IX), where R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl, may be carried out by reaction with a compound of formula (XVII).



10

The process may be carried out in a suitable solvent e.g. an aprotic solvent such as benzene, toluene, dioxane, tetrahydrofuran or *N,N*-dimethylformamide with a suitable base such as sodium *tert*-butoxide or lithium bis(trimethylsilyl)amide in the presence of a suitable palladium catalyst such as PdX_2 , $L_2Pd(0)$ or L_2PdX_2 where X stands for a halogen such as chlorine or bromine and L stands for a suitable ligand such as triphenylphosphine, tri-*o*-tolylphosphine, trifurylphosphine, triphenylarsine or dibenzylidenacetone and with or without an addition of a ligand L' such as triphenylphosphine, tri-*o*-tolylphosphine, trifurylphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (either as a racemate or

as an enantiomer) or triphenylarsine and the reaction may occur at a temperature between +20 °C and +150 °C, resulting in the compound of the formula (IX).

The conversion of (XVI) to (IX) can also proceed via the transformation of (XVII) to an aminostannane or aminoborane using agents such as (*N,N*-diethylamino)tributyltin and tris(dimethylamino)borane in a suitable solvent e.g. an aprotic solvent such as benzene, toluene, dioxan, tetrahydrofuran or *N,N*-dimethylformamide and then using similar conditions as described in the above description, resulting in the compound of the formula (IX).

Compound of formula (IX) may also be prepared by,

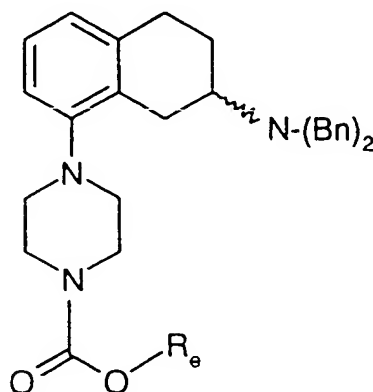
(ix) Alkylation of a compound of formula (XIII), wherein R₁ is hydrogen, with a suitable alkylation reagent such as R₁-L where L is a suitable leaving group e.g. a halogen such as chlorine, bromine or iodine or an alkane- or arenesulfonyloxy group such as a *p*-toluenesulfonyloxy group and R₁ is C₁-C₆ alkyl. The reaction may be carried out in a suitable solvent such as *N,N*-dimethylformamide, acetone, acetonitrile or tetrahydrofuran with a suitable base such as K₂CO₃, NaHCO₃, NaOH or a trialkylamine such as triethylamine. The reaction may be conducted at a temperature between +20 °C and + 120 °C.

Alternatively,

(x) conversion of a compound of formula (XIII), wherein R₁ is hydrogen, to a compound of formula (IX) may be carried out by reductive alkylation with a compound R₁-CHO, where R₁ is hydrogen or C₁-C₅ alkyl, or with a C₃-C₆ cyclic ketone, in the presence of a reductive agent such as sodium cyanoborohydride, sodium borohydride or catalytically with H₂ and a suitable catalyst containing palladium, platinum, rhodium or nickel in a suitable solvent e.g. tetrahydrofuran, dioxane, methanol or ethanol. A proton donor such as *p*-toluenesulfonic acid can be used to catalyze the formation of the imine/enamine and

adjustment of pH to slightly acidic by an appropriate acid such as acetic acid may speed up the reaction, resulting in compound (IX).

(xi) In the case where R_1 is methyl, conversion of a compound of formula (XIII) to a
5 compound of formula (IX) may be carried out by

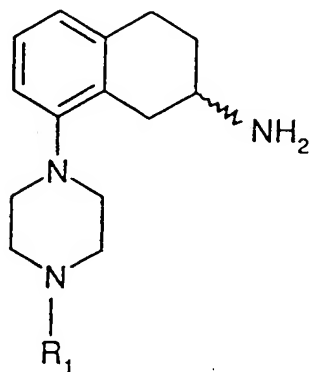


(XLVI)

a) conversion of the compound of formula (XIII) to a compound of formula (XLVI), where
 R_e is C_1 - C_6 alkyl, with a reagent such as an alkyl chloroformate e.g. ethyl chloroformate in
10 a solvent such as methylene chloride, chloroform, dioxane or diethyl ether with a suitable
base such as K_2CO_3 , $NaHCO_3$, $NaOH$ or a trialkylamine such as triethylamine at a reaction
temperature between $-20\text{ }^\circ\text{C}$ and $+60\text{ }^\circ\text{C}$ followed by,

b) reduction of the compound of formula (XLVI) to a compound of formula (IX) with an
15 appropriate reductive agent such as lithium aluminum hydride in a suitable solvent e.g.
diethyl ether or tetrahydrofuran at a temperature between $+20\text{ }^\circ\text{C}$ and reflux.

(xii) Conversion of the compound of formula (IX) to a compound of formula (XII)



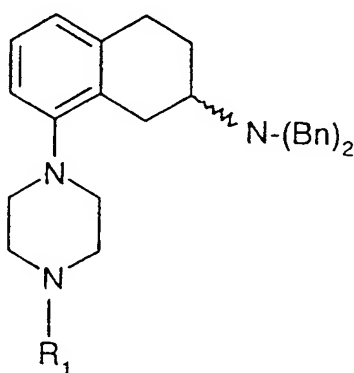
(XII)

5 where R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl may be carried out by

a) hydrogenation using a catalyst containing palladium, platinum, rhodium or nickel in a suitable solvent e.g. acetic acid or ethanol and at a reaction temperature between +20 °C and +120 °C, or

10

b) debenzylation in a suitable solvent such as methanol in the presence of ammonium formate and Pd/C and at a reaction temperature between +20 °C and reflux.

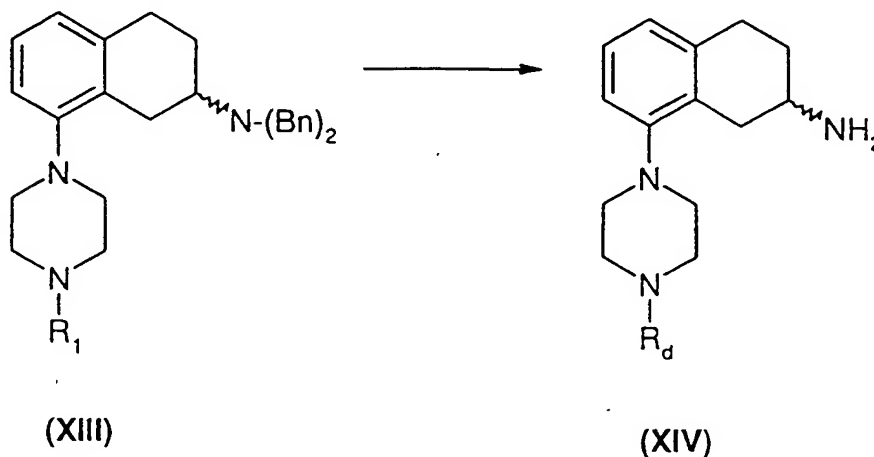


(XIII)

(xiii) In the case when R_1 is hydrogen, conversion of compound of formula (VIII) to a compound of formula (XIII) may be carried out by reaction with a compound of formula (XI) where X stands for a leaving group, e.g. a halogen such as chlorine or bromine or an alkane- or arenesulfonyloxy group such as p-toluenesulfonyloxy group and R_1 is hydrogen.

5 The process may be carried out in a suitable solvent such as ethanol, butanol, *N,N*-dimethylformamide, acetonitrile or a mixture of water and acetonitrile with a suitable base e.g. K_2CO_3 , $NaHCO_3$ or KOH and the reaction may occur between +20 °C and +150 °C.

(xiv) Conversion of a compound of formula (XIII), where R_1 is hydrogen, to a compound of formula (XIV),



where R_d stands for a suitable protecting group, may be carried out by

15

a) hydrogenation using a catalyst containing palladium, platinum, rhodium or nickel in a suitable solvent e.g. acetic acid or ethanol at a reaction temperature between +20 °C and +120 °C, or

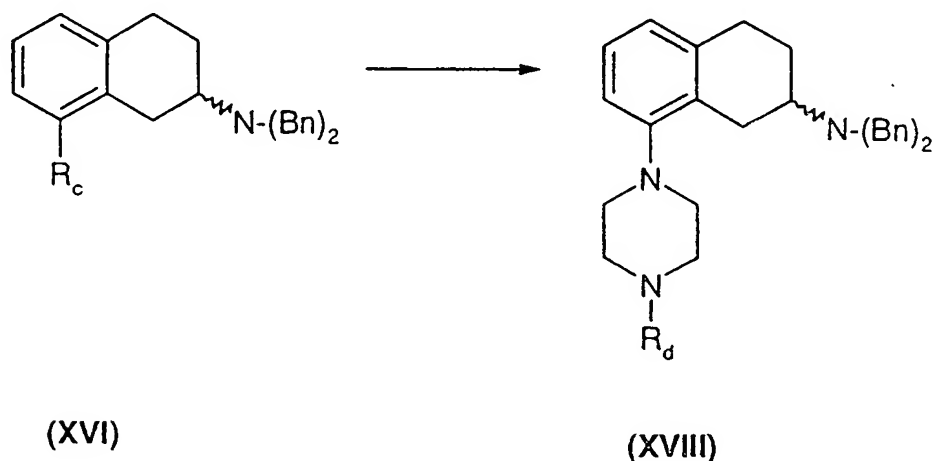
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b) debenzoylation in a suitable solvent such as methanol in the presence of ammonium formate and Pd/C at a reaction temperature between +20 °C and reflux.

Said reaction is followed by the protection of the piperazine ring in a suitable solvent e.g. methylene chloride or chloroform with an appropriate protecting reagent e.g. di-*tert*-butyl dicarbonate with a suitable base e.g. triethylamine or K_2CO_3 and at a temperature between $-20\text{ }^\circ\text{C}$ and $+60\text{ }^\circ\text{C}$, resulting in compound of formula (XIV).

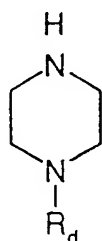
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Alternatively, a compound of formula (XIV) may be prepared by,



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(xv) Conversion of the compound of formula (XVI) to a compound of formula (XVIII), where R_d is a suitable protecting group such as a benzyl or *tert*-butoxycarbonyl group, may be carried out by the reaction with a compound of formula (XIX).



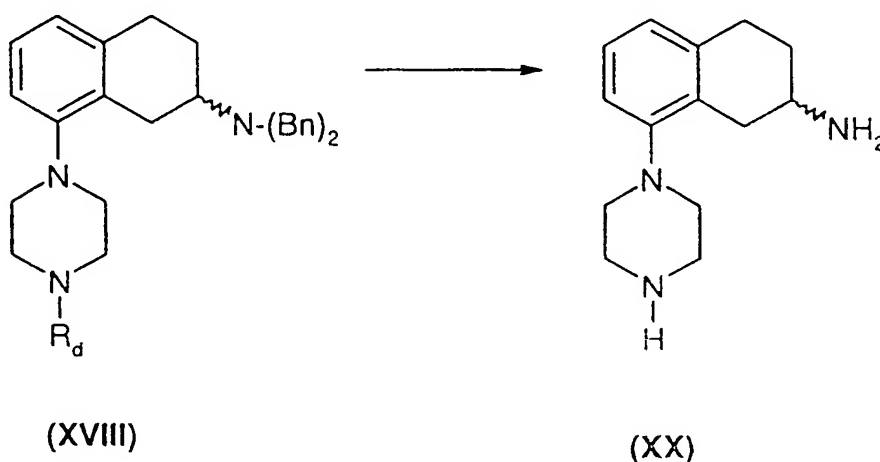
(XIX)

15

The process may be carried out in a suitable solvent e.g. an aprotic solvent such as benzene, toluene, dioxane, tetrahydrofuran or *N,N*-dimethylformamide with a suitable base such as

sodium *tert*-butoxide or lithium bis(trimethylsilyl)amide in the presence of a suitable palladium catalyst such as PdX_2 , $\text{L}_2\text{Pd}(0)$ or L_2PdX_2 where X stands for a halogen such as chlorine or bromine and L stands for a suitable ligand such as triphenylphosphine, tri-*o*-tolylphosphine, trifurylphosphine, triphenylarsine or dibenzylidenacetone and with or
 5 without an addition of a ligand L' such as triphenylphosphine, tri-*o*-tolylphosphine, trifurylphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (either as a racemate or as an enantiomer) or triphenylarsine and the reaction may occur at a temperature between +20 °C and +150 °C, resulting in the compound of the formula (XVIII).

10 The conversion of (XVI) to (XVIII) can also proceed via the transformation of (XIX) to an aminostannane or aminoborane using agents such as (*N,N*-diethylamino)tributyltin and tris(dimethylamino)borane in a suitable solvent e.g an aprotic solvent such as benzene, toluene, dioxane, tetrahydrofuran or *N,N*-dimethylformamide and then using similar conditions as described in the above description, resulting in the compound of the formula
 15 (XVIII).



(xvi) Conversion of the compound of formula (XVIII) to a compound of formula (XX) may
 20 be carried out by removal of the protecting group R_d of the compound of formula (XVIII) by methods known in the art such as

a) hydrolysis of a *tert*-butoxycarbonyl group in a suitable solvent e.g. methylene chloride or chloroform with a suitable acid such as trifluoroacetic acid at a temperature between + 20 °C and +60 °C, followed by

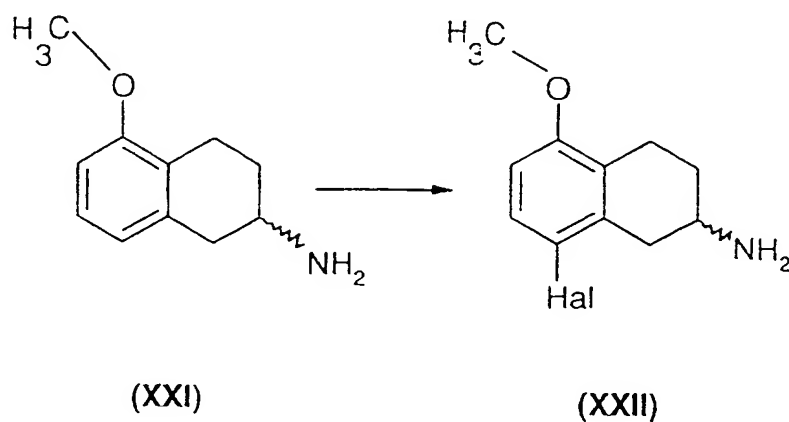
5 b) cleavage of the benzyl groups by hydrogenation over a suitable catalyst containing palladium, rhodium, platinum or nickel, in a suitable solvent e.g. acetic acid or ethanol at a temperature between + 20 °C and + 120 °C, or alternatively by,

c) debenzylation in a suitable solvent such as methanol in the presence of ammonium
10 formate and Pd/C and at a reaction temperature between + 20 °C and reflux.

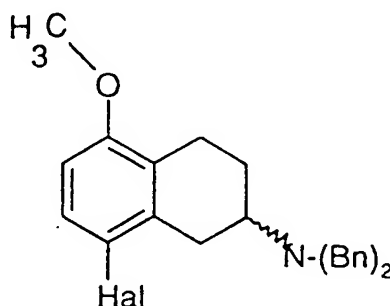
Said reaction is followed by the protection of the piperazine ring in a suitable solvent such as methylene chloride or chloroform with an appropriate protecting reagent e.g. di-*tert*-butyl dicarbonate with a suitable base such as triethylamine or K₂CO₃ at a temperature
15 between - 20 °C and + 60 °C, resulting in the compound of formula (XIV).

2.

20 (i) Halogenation of the compound of formula (XXI), either as a racemate or as an enantiomer



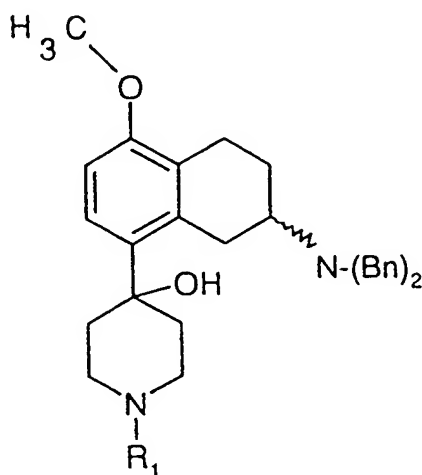
to obtain a compound of formula (XXII) may be performed by aromatic electrophilic substitution using a suitable halogenation agent such as Br₂, Cl₂, I₂, ICl, or SO₂Cl₂. The reaction may be carried out using the salt or the base of the compound (XXI) in an appropriate solvent e.g. acetic acid, HCl/ethanol or water with or without a suitable base e.g. an alkali metal acetate such as sodium acetate and at a reaction temperature between -20 °C and room temperature.



(XXIII)

(ii) Benzylation of the compound of the formula (XXII), either as a racemate or as an enantiomer, to obtain a compound of the formula (XXIII) may be carried out by reaction with a suitable benzylation agent e.g. benzyl halide such as benzyl bromide or benzyl chloride. The reaction may be carried out using the salt or the base of compound (XXII) in a suitable solvent e.g. *N,N*-dimethylformamide, acetone or acetonitrile with a suitable base such as triethylamine, NaOH, NaHCO₃ or K₂CO₃ at a temperature within the range of +20 °C to +150 °C. The presence of a suitable catalyst e.g. an alkali metal halide such as potassium iodide or sodium iodide may increase the speed of the reaction. The nitrogen in compound (XXII) may also be protected by reductive alkylation with an arylaldehyde in the presence of a reductive agent such as sodium cyanoborohydride, sodium borohydride or catalytically with H₂ and a suitable catalyst containing palladium, platinum, rhodium or nickel in a suitable solvent e.g. tetrahydrofuran, dioxane, methanol or ethanol. A proton donor such as *p*-toluenesulfonic acid can be used to catalyze the formation of the

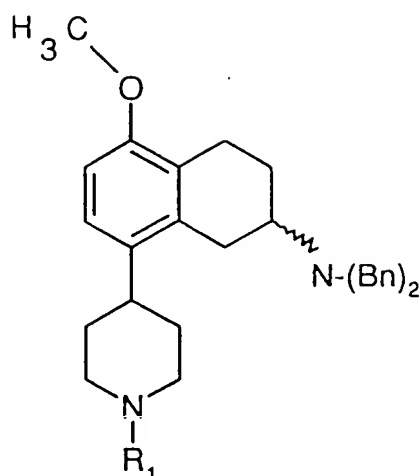
imine/enamine and adjustment of pH to slightly acidic by an appropriate acid such as acetic acid may speed up the reaction, resulting in compound (XXIII).



(XXIV)

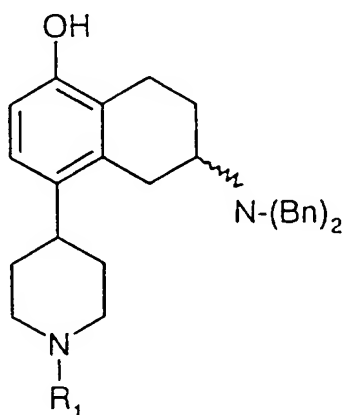
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iii) The conversion of the compound of the formula (XXIII) to the compound of the formula (XXIV), where R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl, may be performed by a metal-halogen exchange, in an appropriate anhydrous solvent such as tetrahydrofuran or diethyl ether using a suitable alkyl-lithium or metal e.g. butyllithium, lithium or magnesium
10 turnings, followed by treatment with an appropriate piperidone such as *N*-methyl-4-piperidone and a subsequent suitable workup. The reaction may be performed at a reaction temperature within the range of -78 °C to room temperature.



(XXV)

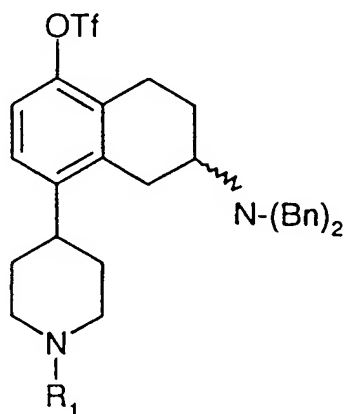
(iv) The compound of the (XXIV) may be reduced to the compound of the formula (XXV) by treatment with a suitable reducing agent such as sodium borohydride and a protonating agent such as CF_3COOH , $\text{CF}_3\text{SO}_3\text{H}$ or HCOOH in an appropriate solvent such as tetrahydrofuran or diethyl ether. The reaction may be performed at reaction temperature between 0°C and reflux.



(XXVI)

(v) Demethylation of the compound of the formula (XXV) to obtain a compound of formula (XXVI) may be performed by treating the compound with an acidic reagent such as aqueous HBr , HI , HBr /acetic acid, BBr_3 , AlCl_3 , pyridine- HCl or with a basic nucleophilic

reagent such as $\text{C}_2\text{H}_5\text{S}^-$ or $\text{CH}_3\text{C}_6\text{H}_4\text{S}^-$ in a suitable solvent. Suitable solvents may be methylene chloride or chloroform and the reaction may occur between -78°C and $+60^\circ\text{C}$.



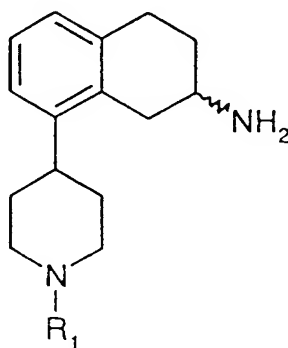
(XXVII)

5

(vi) Conversion of the compound of formula (XXVI) to a compound of formula (XXVII) may be carried out with a compound such as trifluoromethanesulfonic anhydride in a suitable solvent such as methylene chloride or carbon tetrachloride in the presence of a base such as 2,4,6-collidine, triethylamine or pyridine at a reaction temperature within the range

10

of -78°C to room temperature.



(XXVIII)

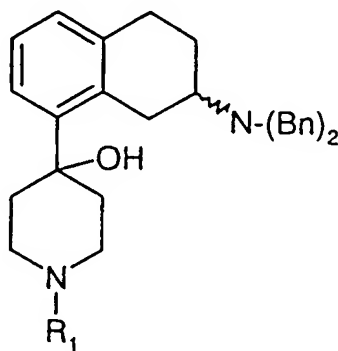
vii) Conversion of the compound of formula (XXVII) to a compound of formula (XXVIII) may be performed by

15

a) hydrogenation using a catalyst such as palladium, platinum, rhodium or nickel in a suitable solvent such as acetic acid or ethanol at a reaction temperature between +20 °C and +120 °C, or

b) reaction in a suitable solvent such as methanol in the presence of ammonium formate and Pd/C at a reaction temperature between +20 °C and reflux.

Alternatively, a compound of formula (XXVIII) may be prepared by,

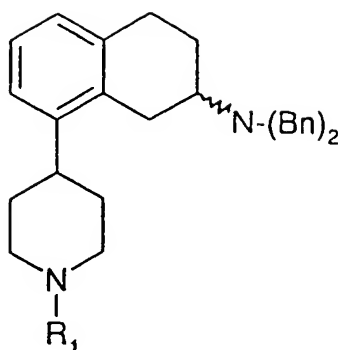


(XXIX)

10

(viii) The conversion of a compound of the formula (XVI), where R_C is a halogen such as bromine, to a compound of the formula (XXIX), where R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl. This may be performed by a metal-halogen exchange, in an appropriate anhydrous solvent such as tetrahydrofuran or diethyl ether using a suitable alkyl-lithium or metal e.g. butyllithium, lithium or magnesium turnings, followed by treatment with appropriate piperidone such as *N*-methyl-4-piperidone and a subsequent suitable workup. The reaction may be performed at a reaction temperature within the range of -78 °C to room temperature.

15



(XXX)

(ix) A compound of the formula (XXIX) may be reduced to a compound of the formula (XXX) by treatment with a suitable reducing agent such as sodium borohydride and a
 5 protonating agent such as CF₃COOH, CF₃SO₃H or HCOOH in an appropriate solvent such as tetrahydrofuran or diethyl ether. The reaction may be performed at a reaction temperature between 0 °C and reflux.

(x) Conversion of a compound of formula (XXX) to a compound of formula (XXVIII),
 10 where R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl, may be performed by

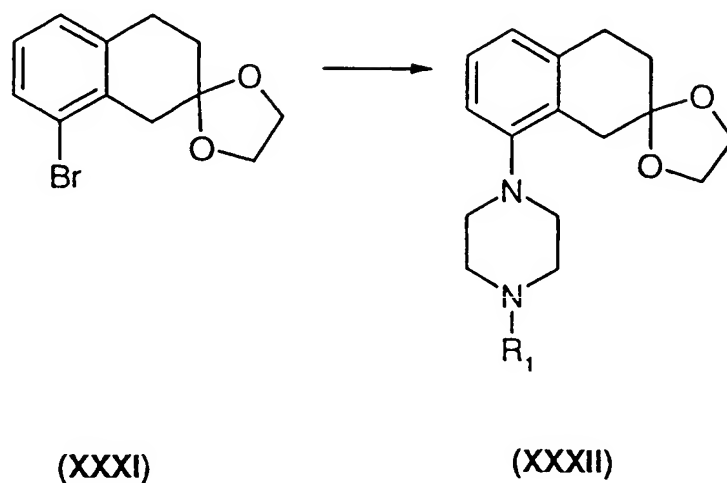
a) hydrogenation using a catalyst containing palladium, platinum, rhodium or nickel in a suitable solvent e.g. acetic acid or ethanol at a reaction temperature between +20 °C and +120 °C, or

15 b) debenzylation in a suitable solvent such as methanol in the presence of ammonium formate and Pd/C and at a reaction temperature between +20 °C and reflux.

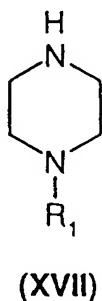
3.

20 (i) Conversion of the compound of formula (XXXI) described in Sunkyung L.; Stewart P. F.; David E. N. *Synth. Commun.* **1995**, 25(18), 2775-2780, where the protected ketone may be protected as other ketals, cyclic or acyclic, or by other protective groups known by a

person skilled in the art (see T.W. Greene, Wiley-Interscience, New York, 1991), to a compound of formula (XXXII)



where R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl, may be carried out by the reaction with a compound of formula (XVII).

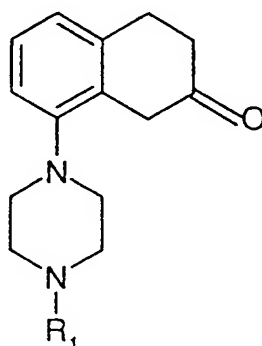


The process may be carried out in a suitable solvent e.g. an aprotic solvent such as benzene, toluene, dioxane, tetrahydrofuran or *N,N*-dimethylformamide with a suitable base such as sodium *tert*-butoxide or lithium bis(trimethylsilyl)amide in the presence of a suitable palladium catalyst such as PdX_2 , $L_2Pd(0)$ or L_2PdX_2 where X stands for a halogen such as chlorine or bromine and L stands for a suitable ligand such as triphenylphosphine, tri-*o*-tolylphosphine, trifurylphosphine, triphenylarsine or dibenzylidenacetone and with or without an addition of a ligand L' such as triphenylphosphine, tri-*o*-tolylphosphine, trifurylphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (either as a racemate or

as an enantiomer) or triphenylarsine and the reaction may occur at a temperature between +20 °C and +150 °C, resulting in the compound of the formula (XXXII).

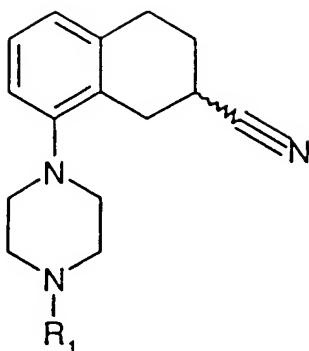
The conversion of (XXXI) to (XXXII) can also proceed via the transformation of (XVII) to
5 an aminostannane or aminoborane using agents such as (*N,N*-diethylamino)tributyltin and
tris(dimethylamino)borane in a suitable solvent e.g an aprotic solvent such as benzene,
toluene, dioxan, tetrahydrofuran or *N,N*-dimethylformamide and then using similar
conditions as described in the above description, resulting in a compound of the formula
(XXXII).

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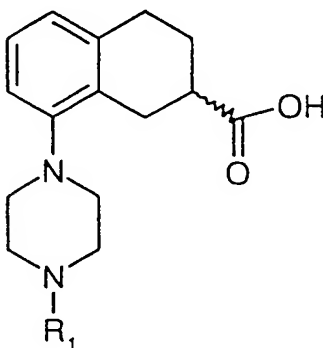
(XXXIII)

(ii) Conversion of a compound of formula (XXXII) to a compound of formula (XXXIII)
may be carried out by using a suitable aqueous acid such as HCl, HBr or acetic acid at a
15 reaction temperature between + 20 °C and reflux or by other methods known by a person
skilled in the art (see T.W. Greene, Wiley-Interscience, New York, 1991).



(XXXIV)

The above reaction is followed by the conversion of the ketone of the formula (XXXIII) to compound of formula (XXXIV) by the reaction with an appropriate cyanation reagent such as tosylmethyl isocyanide in the presence of suitable base e.g. potassium *tert*-butoxide in a suitable solvent such as 1,2- dimethoxyethane, dimethyl sulfoxide or hexamethylphosphoric triamide containing small amounts of an alcohol such as methanol, ethanol or *tert*-butanol at a temperature between 0 °C and + 100 °C or via cyanohydrin formation and then conversion to a compound of formula (XXXIV).

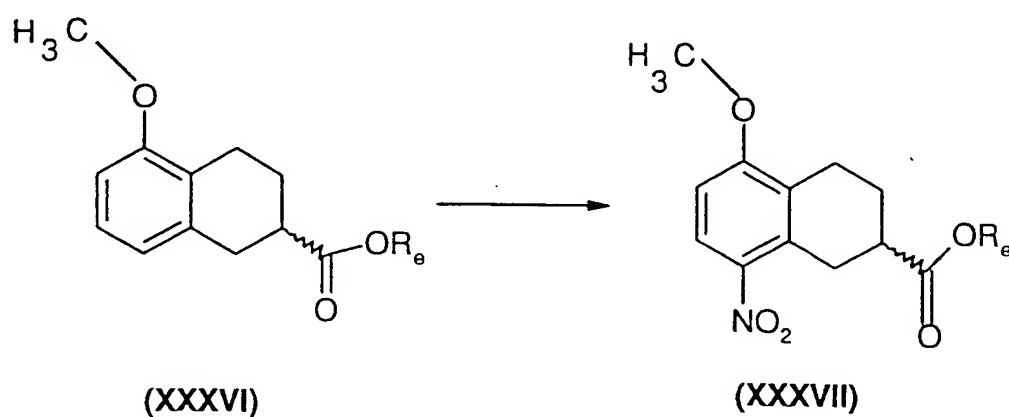


(XXXV)

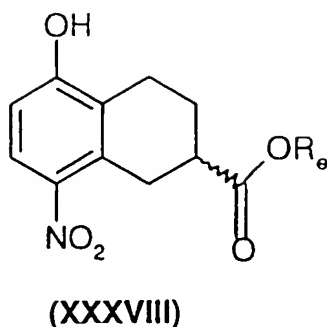
(iii) Hydrolysis of a compound of formula (XXXIV) to a compound (XXXV) may be carried out under acidic conditions using acids such as H₂SO₄, HCl, HBr, in a suitable solvent such as H₂O, ethanol, methanol, acetic acid or mixtures thereof and the reaction may occur at a temperature between + 20 °C and reflux or under basic conditions using bases such as NaOH or KOH in a suitable solvent such as H₂O, ethanol, methanol or mixtures thereof at a temperature between + 20 °C and reflux.

4.

- (i) Nitration of a compound of formula (XXXVI), described in Johnson D.W.; Mander L.N. *Aust. J. Chem* 1974, 27,1277-1286, either as racemate or as an enantiomer, to obtain a compound of formula (XXXVII),



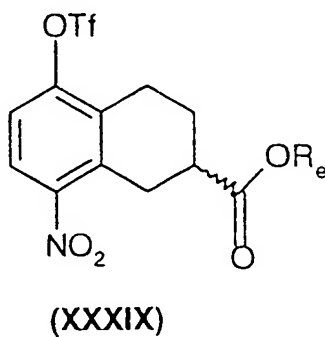
- where R_e is C_1 - C_6 alkyl, may be carried out by aromatic electrophilic substitution using a suitable nitration reagent such as nitric acid or nitric acid and sulfuric acid in a suitable solvent e.g. acetic acid, acetic anhydride or water at a reaction temperature between $-20\text{ }^{\circ}\text{C}$ and room temperature.
- (ii) Demethylation of the compound of the formula (XXXVII) to obtain a compound of formula (XXXVIII)



may be carried out by treating the compound with an acidic reagent such as aqueous HBr, HI, HBr/CH₃COOH, BBr₃, AlCl₃, pyridine-HCl or with a basic nucleophilic reagent such as CH₃C₆H₄S⁻ or C₂H₅S⁻. Suitable solvents may be methylene chloride or chloroform and the reaction may occur between -78 °C and +60 °C.

During the demethylation of (XXXVII), hydrolysis of the ester may occur and the acid function could then be converted back to the ester by methods known by a person skilled in the art (See T.W. Greene, Wiley-Interscience, New York, 1991).

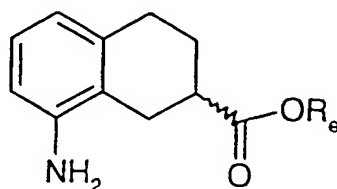
(iii) Conversion of the compound of formula (XXXVIII) to a compound of formula (XXXIX)



may be carried out by the reaction with an activated trifluoromethanesulfonic reagent e.g. trifluoromethanesulfonic anhydride in a suitable solvent such as methylene chloride,

chloroform or carbon tetrachloride in the presence of a suitable base such as triethylamine, pyridine or 2,4,6-collidine at a reaction temperature between -78 °C and room temperature.

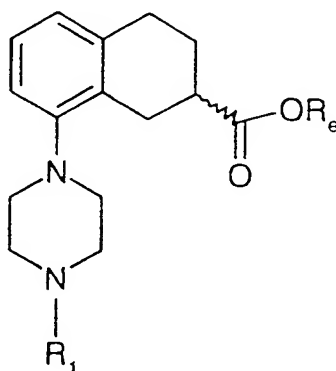
- (iv) Conversion of the compound of formula (XXXIX) to a compound of formula (XL)
5 may be carried out by



(XL)

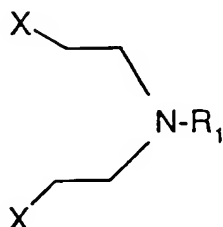
- a) hydrogenation using a catalyst containing palladium, platinum or nickel in a suitable
10 solvent such as ethanol, methanol or acetic acid and at a reaction temperature between + 20 °C and + 120 °C or
- b) reaction in a suitable solvent such as methanol in the presence of a ammonium formate such as triethyl ammonium formate and Pd/C and at a reaction temperature between + 20
15 °C and reflux.

- (v) Conversion of the compound of formula (XL) to a compound of formula (XLI)



(XLI)

may be carried out by reaction of compound (XI)

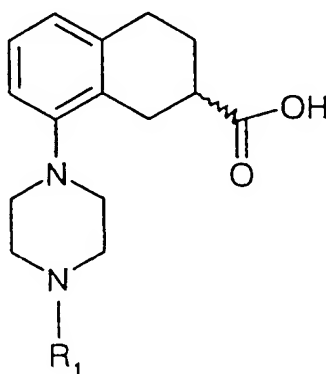


(XI)

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where X stands for a leaving group, e.g. a halogen such as chlorine or bromine or an alkane- or arenesulfonyloxy group such as p-toluene-sulfonyloxy group and R₁ is hydrogen, C₁-C₆ alkyl or C₃-C₆ cycloalkyl. The process may be carried out in a suitable solvent such as ethanol, butanol, *N,N*-dimethylformamide, acetonitrile or a mixture of water and
 10 acetonitrile with a suitable base e.g. K₂CO₃, NaHCO₃ or KOH and the reaction may occur between +20 °C and +150 °C.

During the cyclization reaction of (XL), hydrolysis of the ester may occur.



(XXXV)

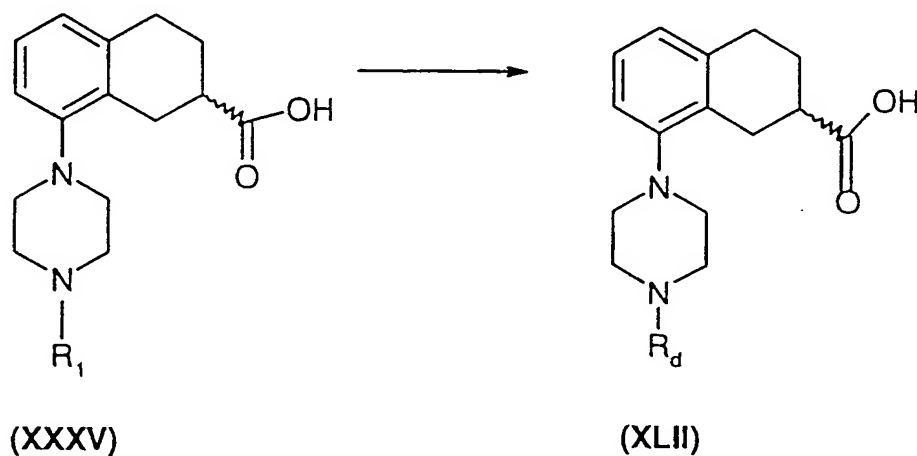
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(vi) Hydrolysis of a compound of formula (XLI) may be carried out under acidic conditions using acids such as H₂SO₄, HCl, HBr, in a suitable solvent such as H₂O, ethanol, methanol, acetic acid or mixtures thereof at a temperature between + 20 °C and reflux or under basic

conditions using bases such as NaOH or KOH in a suitable solvent such as H₂O, ethanol, methanol or mixtures thereof at a temperature between + 20 °C and reflux, resulting in a compound of formula (XXXV), where R₁ is hydrogen, C₁-C₆ alkyl or C₃-C₆ cycloalkyl.

5

(vii) When R₁ is hydrogen, protection of a compound of formula (XXXV) as a compound of formula (XLII) where R_d is a protecting group

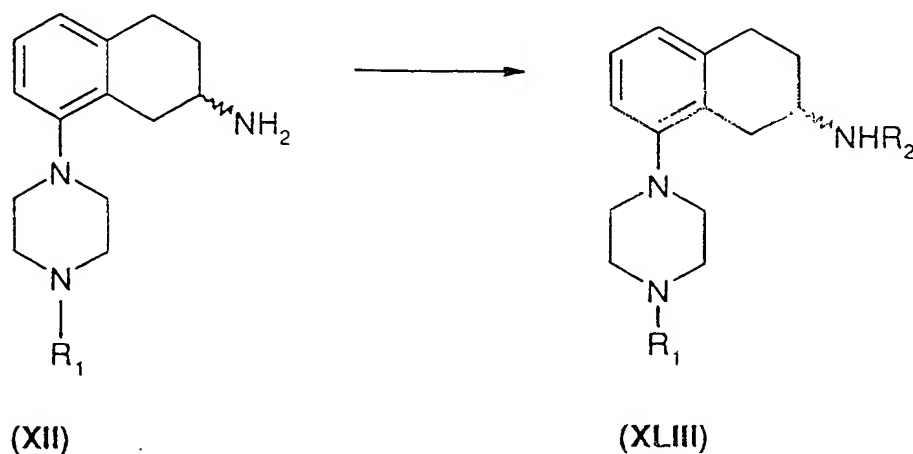


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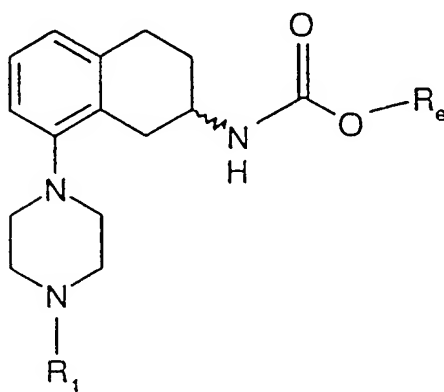
may be carried out by the reaction with a suitable protecting reagent such as di-*tert*-butyl dicarbonate in a suitable solvent e.g methylene chloride or chloroform with a suitable base such as triethylamine or K₂CO₃ and at a temperature between - 20 °C and + 60 °C.

15

5.



- (i) Conversion of a compound of formula (XII), where R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl, to a compound of formula (XLIII) may be carried out by the alkylation of compound of formula (XII) with a suitable alkylation reagent such as R_2 -Z where Z is a suitable leaving group e.g. a halogen such as chlorine, bromine or iodine or an alkane- or arenesulfonyloxy group such as p-toluenesulfonyloxy group and R_2 is C_1 - C_6 alkyl. The reaction may be carried out in a suitable solvent such as *N,N*-dimethylformamide, acetone, acetonitrile or tetrahydrofuran with a suitable base such as K_2CO_3 , $NaHCO_3$, $NaOH$ or a trialkylamine such as triethylamine. The reaction may be conducted at a temperature between $+20\text{ }^\circ\text{C}$ and $+120\text{ }^\circ\text{C}$.
- (ii) In the case where R_2 is methyl, conversion of compound of formula (XII) to a compound of formula (XLIII) may be carried out by



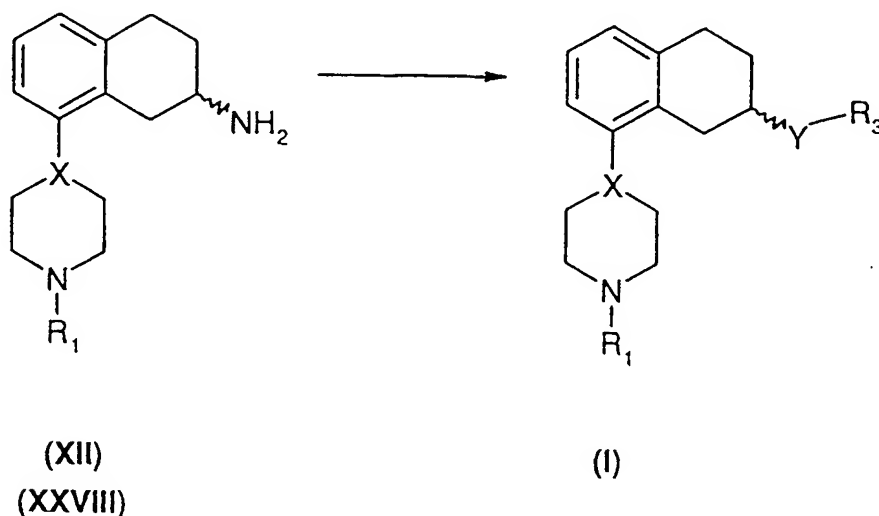
(XLIV)

- a) conversion of the compound of formula (XII) to a compound of formula (XLIV), where R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl and R_e is C_1 - C_6 alkyl, with a reagent such as an alkyl chloroformate e.g. ethyl chloroformate in a solvent such as methylene chloride, chloroform, dioxane or diethyl ether with a suitable base such as K_2CO_3 , $NaHCO_3$, $NaOH$ or a trialkylamine such as triethylamine at a reaction temperature between $-20\text{ }^\circ\text{C}$ and $+60\text{ }^\circ\text{C}$ followed by,

b) reduction of compound of formula (XLIV) to a compound of formula (XLIII) with an appropriate reductive agent such as lithium aluminum hydride in a suitable solvent e.g. diethyl ether or tetrahydrofuran at a temperature between +20 °C and reflux.

Methods of Preparation of End Products

Method A(i):

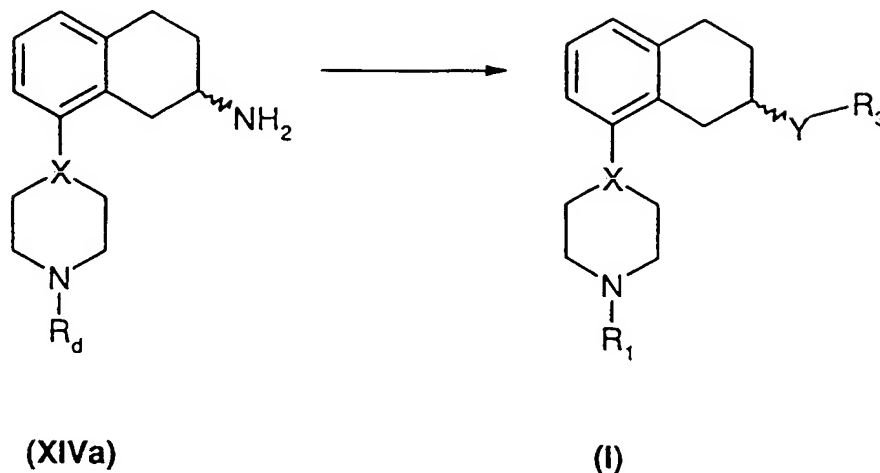


Acylation of the compound of formula (XII) wherein X is N or (XXVIII) wherein X is CH and R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl, may be carried out with an appropriate activated carboxylic acid, R₃-COL where R₃ is as defined in claim 1 and L is a leaving group such as a halogen e.g. chlorine, in a suitable solvent such as methylene chloride or chloroform with a suitable base e.g. trialkylamine such as triethylamine at a temperature between -20 °C and reflux temperature or by using a carboxylic acid, R₃-COOH, where R₃ is as defined in claim 1 with an activating reagent e.g. *N,N'*-carbonyldiimidazole or *N,N'*-dicyclohexylcarbodiimide in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofuran and the reaction may be conducted at a temperature between +20 °C and +150 °C, resulting in the compound of the formula (I) according to the invention, wherein

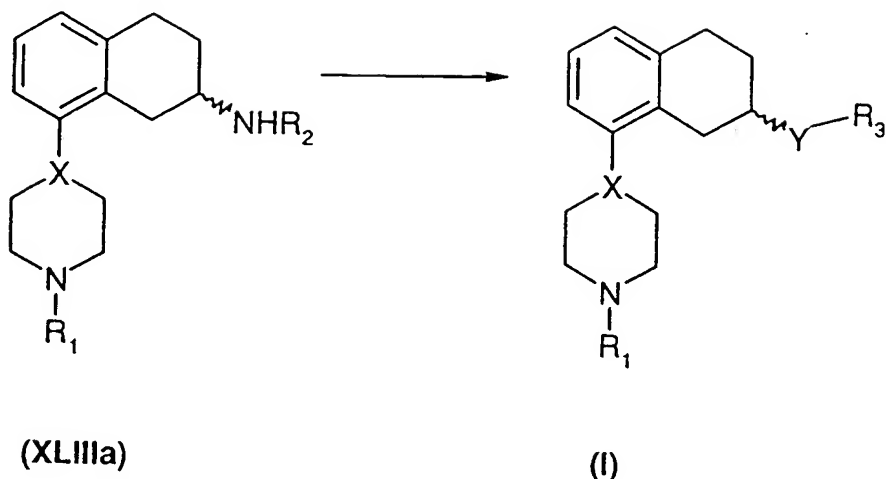
Y is NR_2CO , where R_2 is hydrogen, and X is N or CH and R_1 is $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl, and R_3 is as in claim 1.

Method A(ii):

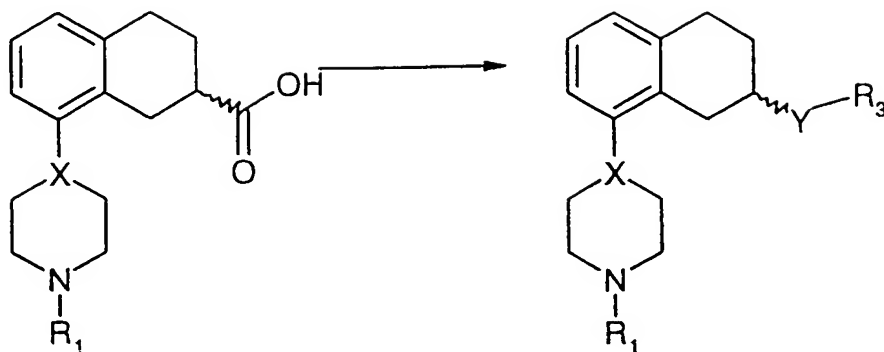
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Acylation of the compound of formula (XIVa), wherein X is N or CH and R_d is a protecting group, may be carried out with an appropriate activated carboxylic acid $\text{R}_3\text{-COL}$, where R_3 is as defined in claim 1 and L is a leaving group such as a halogen e.g. chlorine, in a suitable solvent such as methylene chloride or chloroform with a suitable base e.g. trialkyl amine such as triethylamine at a temperature between -20°C and reflux temperature or by using a carboxylic acid, $\text{R}_3\text{-COOH}$, where R_3 is as defined in claim 1 with an activating reagent e.g. N,N' -carbonyldiimidazole or N,N' -dicyclohexylcarbodiimide in a suitable solvent such as N,N -dimethylformamide or tetrahydrofuran at a temperature between $+20^\circ\text{C}$ and $+150^\circ\text{C}$, followed by removal of the protecting group R_d by hydrolysis in a suitable solvent such as methylene chloride or chloroform with a suitable acid such as trifluoroacetic acid at a temperature between $+20^\circ\text{C}$ and $+60^\circ\text{C}$, resulting in a compound of the formula (I) according to the invention, wherein Y is NR_2CO , R_1 and R_2 are hydrogen, X and R_3 are as in claim 1.

Method A(iii)

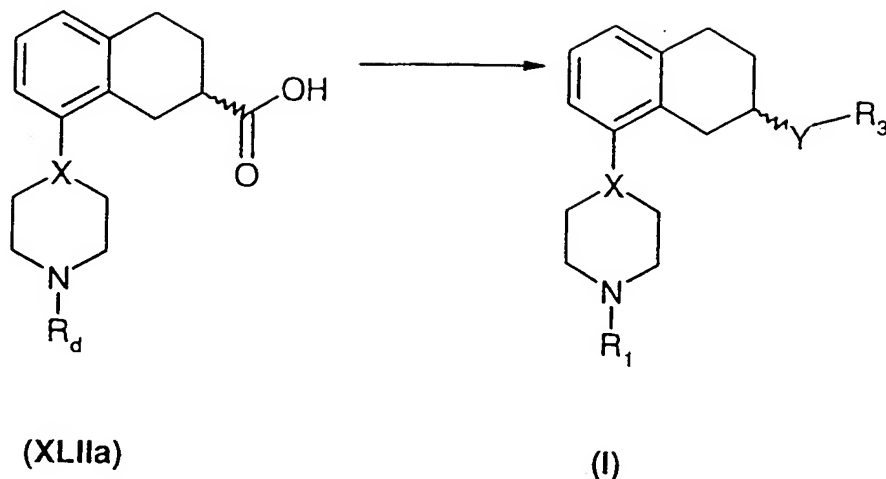
5 Acylation of the compound of formula (XLIIIa), wherein X is N or CH, R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl, R₂ is C₁-C₆ alkyl may be carried out with an appropriate activated carboxylic acid R₃-COL, where R₃ is as defined in claim 1 and L is a leaving group such as a halogen e.g. chlorine, in a suitable solvent such as methylene chloride or chloroform with a suitable base e.g. trialkyl amine such as triethylamine at a temperature between -20 °C and reflux temperature by using a carboxylic acid, R₃-COOH, where R₃ is as defined in claim 1
 10 or by using an activating reagent e.g. *N,N'*-carbonyldiimidazole or *N,N'*-dicyclohexylcarbodiimide in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofuran at a temperature between +20 °C and +150 °C, resulting in a compound of the formula (I) according to the invention, wherein Y is NR₂CO, R₂ is C₁-C₆ alkyl, R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl and X and R₃ are as in claim 1.

Method B(i)

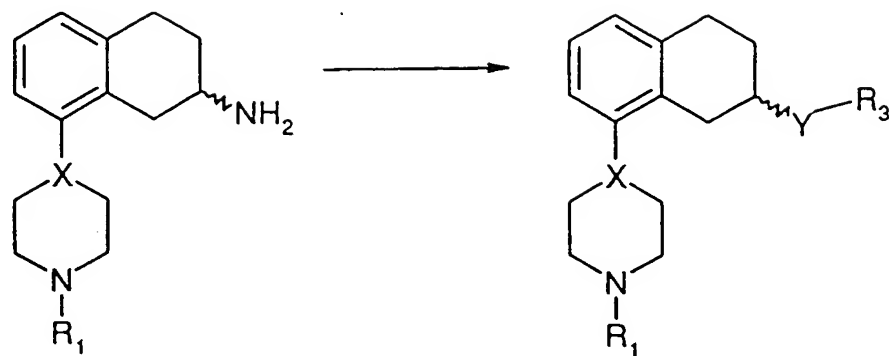
(XXXVa)

(I)

Conversion of a compound of formula (XXXVa), wherein X is N or CH and R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl, to a compound of formula (I) according to the invention, wherein
 5 Y is CONR₂, R₂ is hydrogen or C₁-C₆ alkyl, R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl and X and R₃ are as in claim 1, may be carried out by activation of the acid function of a compound of formula (XXXVa) as an acid halide such as an acid chloride or by using an activating reagent such as *N,N'*-carbonyldiimidazole or *N,N*-dicyclohexylcarbodiimide in a
 10 suitable solvent e.g. methylene chloride, chloroform, toluene, *N,N*-dimethylformamide, dioxane or tetrahydrofuran followed by the addition of an appropriate amine or aniline HNR₂R₃ and the reaction may occur between 0 °C and + 120 °C.

Method B(ii)

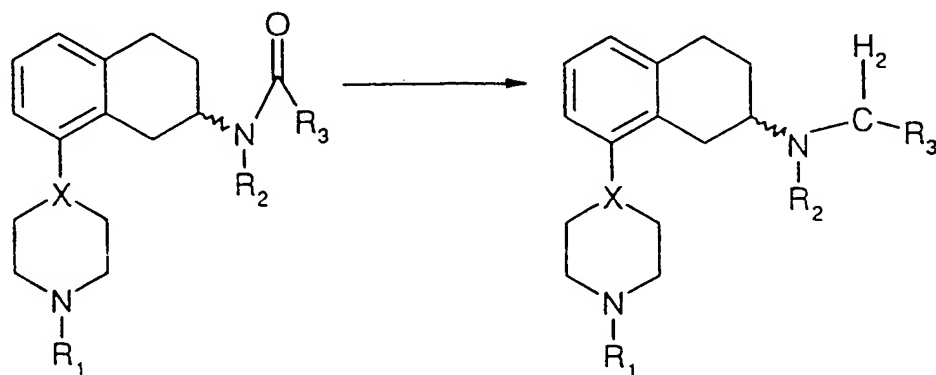
- 5 Conversion of a compound of formula (XLIIa), wherein X is N or CH and R_d is a protecting group, to a compound of formula (I) according to the invention, wherein Y is CONR_2 , R_2 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl, R_1 is hydrogen and X and R_3 are as in claim 1, may be carried out by activation of the acid function of a compound of formula (XLIIa) as an acid halide such as an acid chloride or by using an activating reagent such as *N,N'*-
- 10 carbonyldiimidazole or *N,N*-dicyclohexylcarbodiimide in a suitable solvent e.g. methylene chloride, chloroform, toluene, *N,N*-dimethylformamide, dioxane or tetrahydrofuran followed by the addition of an appropriate amine or aniline HNR_2R_3 and the reaction may occur between 0°C and $+120^\circ\text{C}$, followed by removal of the protecting group R_d by methods known by a person skilled in the art such as hydrolysis in a suitable solvent such as
- 15 methylene chloride or chloroform with a suitable acid e.g. trifluoroacetic acid at a temperature between $+20^\circ\text{C}$ and $+60^\circ\text{C}$.

Method C

(XIIa)

(I)

Conversion of a compound of formula (XIIa), wherein X is N or CH and R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl, to a compound of formula (I) according to the invention, wherein Y is NR₂SO₂, R₂ is hydrogen, R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl and X and R₃ are as in claim 1, may be carried out by reaction with an appropriate activated sulfonic acid R₃SO₂L, where L is a leaving group such as a halogen e.g. a chlorine in a suitable solvent such as methylene chloride or chloroform with a suitable base e.g. trialkyl amine such as triethylamine and the reaction may be conducted at a temperature between -20 °C and +60 °C.

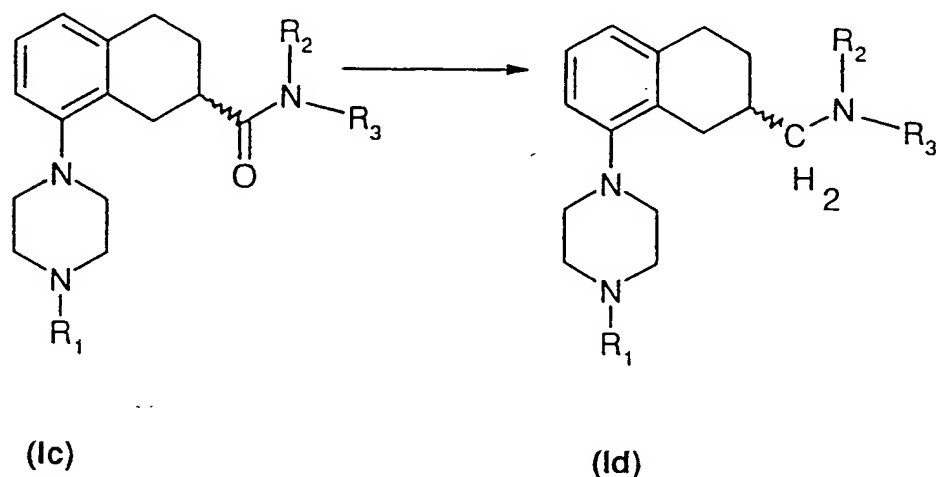
Method D(i)

(Ia)

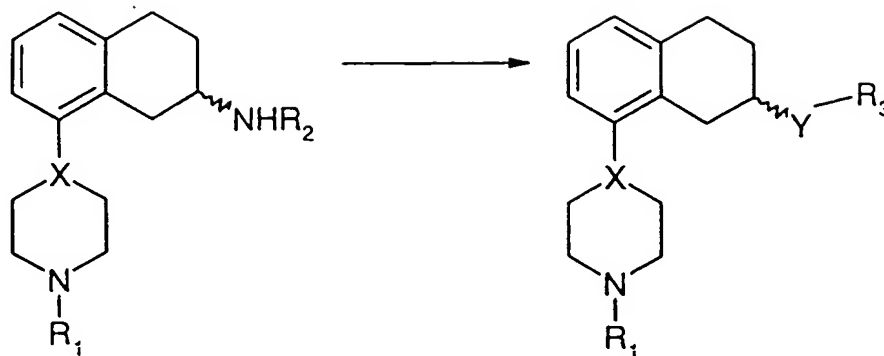
(Ib)

Reduction of a compound of formula (I), according to the invention wherein X is N or CH, Y is NR_2CO , R_2 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl, R_1 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl and X and R_3 are as in claim 1 (above denoted (Ia)) obtained by methods A(i), A(ii) or A(iii) above, to a compound of formula (I) according to the invention where Y is NR_2CH_2 and X, R_1 , R_2 and R_3 are as defined above (above denoted (Ib)) may be carried out with an appropriate reductive agent such as lithium aluminum hydride in a suitable solvent e.g. diethyl ether or tetrahydrofuran at a temperature between $+20^\circ\text{C}$ and reflux temperature.

10 **Method D(ii)**



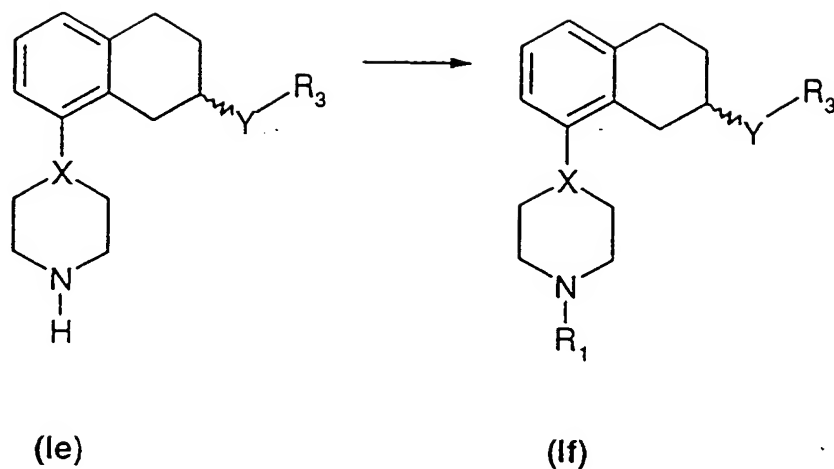
Reduction of a compound of formula (I) according to the invention wherein X is N or CH, Y is CONR_2 , R_2 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl, R_1 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl and X and R_3 are as in claim 1, (above denoted (Ic)) and obtained by methods B(i) or B(ii) above, to a compound of formula (I) according to the invention wherein Y is CH_2NR_2 , X, R_1 , R_2 and R_3 are as defined in claim 1 (above denoted (Id)) may be carried out with an appropriate reductive agent such as lithium aluminum hydride in a suitable solvent e.g. diethyl ether or tetrahydrofuran at a temperature between $+20^\circ\text{C}$ and reflux temperature.

Method E

(XIIa),(XIVa),(XLIa)

(I)

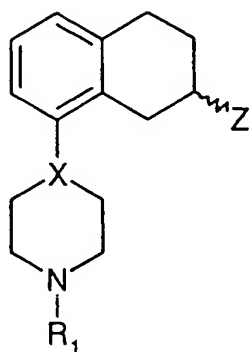
Alkylation of compound of formula (XIIa), wherein X is N or CH, R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl, R₂ is hydrogen, or a compound of formula (XIVa), wherein X is N or CH, R₁ is R_d, where R_d is a protecting group, and R₂ is hydrogen, or a compound of formula (XLIa), wherein X is N or CH, R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl and R₂ is C₁-C₆ alkyl to a compound of formula (I), according to the invention, wherein Y is NR₂CH₂, X, R₁ and R₂ are as above, and R₃ is as in claim 1 may be carried out with a suitable alkylation reagent such as R₃CH₂-L, where L is a suitable leaving group e.g. a halogen such as chlorine, bromine or iodine or an alkyl- or arylsulfonyloxy group such as p-toluene sulfonyloxy group. The reaction may be carried out in a suitable solvent such as *N,N*-dimethylformamide, acetone, acetonitrile or tetrahydrofuran with a suitable base such as K₂CO₃, NaHCO₃, NaOH or a trialkylamine such as triethylamine. The reaction may be conducted at a temperature between +20 °C and +120 °C. In the case when R₁ is R_d, the alkylation is followed by removal of the protecting group R_d by hydrolysis in a suitable solvent such as methylene chloride or chloroform with a suitable acid such as trifluoroacetic acid at a temperature between +20 °C and +60 °C.

Method F

- 5 Alkylation of a compound of formula (Ie), according to the invention wherein X is N or CH, Y is NR₂CO, R₂ is hydrogen or C₁-C₆ alkyl and R₃ is as in claim 1, and obtained by method A(ii), to a compound of formula (If) according to the invention wherein Y is NR₂CO, R₂ is hydrogen or C₁-C₆ alkyl, R₁ is C₁-C₆ alkyl and X and R₃ are as in claim 1 may be carried out with a suitable alkylation reagent such as R₁-L where L is a suitable
- 10 leaving group e.g. a halogen such as chlorine, bromine or iodine or an alkyl- or arylsulfonyloxy group such as p-toluenesulfonyloxy group and R₁ is C₁-C₆ alkyl. The reaction may be carried out in a suitable solvent such as *N,N*-dimethylformamide, acetone, acetonitrile or tetrahydrofuran with a suitable base such as K₂CO₃, NaHCO₃, NaOH or a trialkylamine such as triethylamine. The reaction may be conducted at a temperature
- 15 between +20 °C and +120 °C.

Intermediates

The present invention also refers to new intermediates, namely intermediates of formula



5 wherein

Z= NH₂ or COOH,

X= CH or N, and

R₁= H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

10 The invention is illustrated by but not restricted to the following working examples.

Except where otherwise indicated, the necessary starting materials for all Preparations and Examples were purchased commercially.

15 Working Examples

Example 1

(R)-2-N,N-Dibenzylamino-8-methoxy-1,2,3,4-tetrahydronaphthalene

To a solution of (R)-8-methoxy-2-amino-1,2,3,4-tetrahydronaphthalene hydrochloride
20 (24 g, 0.11 mol) in acetonitrile (600 mL) were added potassium carbonate (53 g, 0.39 mol), potassium iodide (catalytic amount) and benzyl bromide (34 mL, 0.28 mol). The reaction mixture was stirred at reflux for a period of 35 h.

After the precipitate was filtered off and the acetonitrile removed *in vacuo*, the residue was partitioned between diethyl ether and water. The organic phase was separated, dried

(Na₂SO₄) and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using hexane/ethyl acetate, (3:1) as the eluent. Yield: 36 g (91%) of the title compound as a white solid: mp 105-107 °C; [α]²¹_D +124° (*c* 1.0, chloroform); EIMS (70 eV) *m/z* (relative intensity) 357 (100, M⁺).

5

Example 2

(S)-2-N,N-Dibenzylamino-8-methoxy-1,2,3,4-tetrahydronaphthalene

The title compound was synthesized according to the procedure of Example 1 using the (S)-form: mp 106-107 °C; [α]²¹_D -118° (*c* 1.0, chloroform); EIMS (70 eV) *m/z* (relative intensity) 357 (100, M⁺).

10

Example 3

(R)-7-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthol

(R)-2-N,N-Dibenzylamino-8-methoxy-1,2,3,4-tetrahydronaphthalene (43 g, 0.12 mol) was dissolved in diethyl ether (800 mL) and an excess of an ethereal HCl solution was added dropwise. The precipitate was filtered and dried *in vacuo* to give a white solid. This crude product (42 g, 0.11 mol)

15

was dissolved in anhydrous methylene chloride (1 L) and cooled to -60 °C. To the solution was boron tribromide (16 mL, 0.15 mol), dissolved in anhydrous methylene chloride (100 mL), added dropwise. The reaction temperature was allowed to reach -5 °C and was kept there overnight.

20

To the ice-cooled solution was a 2 M aqueous ammonium hydroxide solution added dropwise and the mixture was extracted, twice, with methylene chloride. The combined organic phases were dried (Na₂SO₄), filtered and the solvent removed *in vacuo* to give a crude residue. Chromatography on silica (eluent: methylene chloride) gave 34 g (93% yield) of the title compound as a viscous clear oil: [α]²¹_D +118° (*c* 1.5, chloroform); EIMS (70eV) *m/z* (relative intensity) 343 (53, M⁺).

25

Example 4**(S)-7-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthol**

The title compound was synthesized according to the procedure of Example 3 using the (S)-form: $[\alpha]^{21}_{\text{D}} -116^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 343 (100, M^{+}).

Example 5**(R)-2-(7-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyloxy)-2-methylpropanamide**

(R)-2-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthol (10 g, 29 mmol) was stirred in anhydrous dioxane (150 mL) with sodium hydride (80% in oil, 0.96 g, 32 mmol) for 1 h. 2-Bromo-2-methylpropanamide (4.8 g, 29 mmol; described in: Coutts, I. G. C.; Southcott, M.R. *J. Chem. Soc. Perkin Trans. I* **1990**, 767-770) was added and the reaction mixture was heated at 100 °C for 2.5 h. After cooling, the precipitated sodium bromide was filtered off, the filtrate evaporated *in vacuo* and the residue was partitioned between water and methylene chloride. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give a crude product which was purified on a silica gel column using methylene chloride as the eluent. Yield: 9.6 g (76%) of the title compound as white crystals: mp 125-126 °C; $[\alpha]^{21}_{\text{D}} +98^{\circ}$ (*c* 1.1, chloroform); EIMS (70eV) *m/z* (relative intensity) 428 (13, M^{+}).

Example 6**(S)-2-(7-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyloxy)-2-methylpropanamide**

The title compound was synthesized according to the procedure of Example 5 using the (S)-form: mp 124-125 °C; $[\alpha]^{21}_{\text{D}} -100^{\circ}$ (*c* 0.52, chloroform); EIMS (70eV) *m/z* (relative intensity) 428 (4, M^{+}).

Example 7**(R)-N-(7-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-2-hydroxy-2-methylpropanamide**

To a solution of (R)-2-(7-N,N-dibenzylamino-5,6,7,8-tetrahydro-1-naphthyloxy)-2-methylpropanamide (9.1 g, 21 mmol) in anhydrous 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (10 mL) and dry N,N-dimethylformamide (100 mL) was added sodium hydride (80% in oil, 1.4 g, 47 mmol) and the reaction was heated at 130 °C for 8 h. The solution was poured into a mixture of ice and water and extracted three times with ethyl acetate. The combined organic phases were dried (Na₂SO₄), filtered and evaporated *in vacuo*.

Chromatography on silica (eluent: chloroform/ethanol saturated with NH₃; 100:0.5) gave 7.6 g (84% yield) as white crystals: mp 134-135 °C; [α]²¹_D +130° (c 1.1, chloroform); EIMS (70eV) *m/z* (relative intensity) 428 (1, M⁺).

Example 8**(S)-N-(7-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-2-hydroxy-2-methylpropanamide**

The title compound was synthesized according to the procedure of Example 7 using the (S)-form: mp 132-134 °C; [α]²¹_D -132° (c 0.53, chloroform); EIMS (70eV) *m/z* (relative intensity) 428 (<1, M⁺).

Example 9**(R)-2-N,N-Dibenzylamino-8-amino-1,2,3,4-tetrahydronaphthalene****(R)-N-(7-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-2-hydroxy-2-**

methylpropionamide (7.4 g, 17 mmol) was dissolved in a mixture of ethanol (200 mL) and a 20% HCl aqueous solution (300 mL) and heated to reflux for 8 h. The ethanol was evaporated *in vacuo* and the remaining solution was washed twice with diethyl ether and cooled on ice-bath. After alkalization with a 45% aqueous solution of sodium hydroxide the mixture was extracted with methylene chloride. The combined organic phases were dried (Na₂SO₄), filtered and evaporated *in vacuo*. Purification on a silica gel column using

chloroform as the eluent gave 3.8 g (76% yield) of the title compound as a light-brown oil:
[α]_D²¹ +124° (c 0.9, chloroform); EIMS (70eV) *m/z* (relative intensity) 342 (92, M⁺).

Example 10

(S)-2-N,N-Dibenzylamino-8-amino-1,2,3,4-tetrahydronaphthalene

The title compound was synthesized according to the procedure of Example 9 using the (S)-form: [α]_D²¹ -127° (c 0.53, chloroform); EIMS (70eV) *m/z* (relative intensity) 342 (89, M⁺).

Example 11

(R)-1-(7-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-4-N-methylpiperazine-2,6-dione

1,1'-Carbonyldiimidazole (6.0 g, 37 mmol) was added to a stirred suspension of methyliminodiacetic acid (2.7 g, 18 mmol) in anhydrous tetrahydrofuran (250 mL). The reaction mixture was heated at reflux for 1.5 h. (R)-2-N,N-Dibenzylamino-8-amino-1,2,3,4-tetrahydronaphthalene (5.7 g, 17 mmol) was then added and stirring at reflux was continued for 17 h. An additional amount of 1,1'-carbonyldiimidazole (2.9 g, 18 mmol) was added and heating at reflux was continued for another 17 h. The solvent was evaporated *in vacuo* and the crude product was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:0.5) as the eluent. Yield: 6.6 g (87%) of the title compound as an oil:
[α]_D²¹ +90° (c 0.52, chloroform); EIMS (70eV) *m/z* (relative intensity) 453 (8, M⁺).

Example 12

(R)-2-N,N-Dibenzylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene

(R)-1-(7-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-4-methylpiperazine-2,6-dione (1.4 g, 3.1 mmol) was added to a suspension of lithium aluminium hydride (0.57 g, 15 mmol) in anhydrous diethyl ether (70 mL). The reaction mixture was heated at reflux for 7 h. The reaction was quenched by the addition of water (0.60 mL), 15% aqueous sodium hydroxide (0.60 mL) and again water (1.8 mL). The mixture was filtered, dried (Na₂SO₄) and evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol

saturated with NH₃ (100:2) as the eluent gave 1.0 g (79% yield) of the title compound as a viscous oil: $[\alpha]^{21}_{\text{D}} +53^{\circ}$ (c 0.5, chloroform); EIMS (70 eV) m/z (relative intensity) 425 (2, M⁺).

5 **Example 13**

(S)-2-*N,N*-Dibenzylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (S)-2-*N,N*-Dibenzylamino-8-amino-1,2,3,4-tetrahydronaphthalene (3.0 g, 8.8 mmol), potassium iodide (73 mg, 0.4 mmol) and *N*-methylbis(2-chloroethyl)amine hydrochloride (3.4 g, 17.6 mmol) were mixed with acetonitrile (100 mL) and water (17 mL) under
10 nitrogen atmosphere. The mixture was refluxed for 7h. The temperature of the reaction mixture was allowed to reach room temperature before 2 M sodium hydroxide (20 mL) was added. The solvent was removed *in vacuo* until ca 70 mL remained. The residue was extracted with ethyl acetate twice. The organic layers were combined and dried (Na₂SO₄). Removal of solvent *in vacuo* gave a crude product which was purified on a silica gel column
15 using methylene chloride/ethanol/concentrated ammonium hydroxide (90:9.5:0.5) as the eluent. Yield: 2 g (53%) of the title compound as an oil: $[\alpha]^{21}_{\text{D}} -60^{\circ}$ (c 1, MeOH); EIMS (70eV) m/z (relative intensity) 425 (0.2, M⁺).

Example 14

20 **(R)-2-Amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

To a solution of (R)-2-*N,N*-dibenzylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (4.0 g, 9.4 mmol) in methanol (250 mL) were added ammonium formate (14 g, 56 mmol) and palladium (10%) on activated carbon (1.4 g). The mixture was refluxed for 3 h and the palladium was then filtered off. The solvent was evaporated *in*
25 *vacuo* and the residue was partitioned between methylene chloride and a 2 M ammonium hydroxide solution. The organic phase was separated, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (90:9:0.5) as the eluent. Yield: 1.9 g (83%) as an oil: $[\alpha]^{21}_{\text{D}} -2.7^{\circ}$ (c 1.0, chloroform); EIMS (70 eV) m/z (relative intensity)
30 245 (5, M⁺).

Alternative method:

(*R*)-2-*N,N*-Dibenzylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (1.0 g, 2.4 mmol) was dissolved in glacial acetic acid (70 mL) and palladium (10%) on activated carbon (100 mg) was added and the mixture was hydrogenated at 50-55 °C. The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was dissolved in water (20 mL) and cooled on ice-bath. After alkalization with a 2 M aqueous sodium hydroxide solution the mixture was extracted, twice, with methylene chloride. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude product was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (90:9:0.5) as the eluent to give 330 mg (57% yield) of the title compound.

Example 15**(*S*)-2-Amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

(*S*)-2-*N,N*-Dibenzylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (0.8 g, 1.9 mmol), palladium on activated carbon (10%, 400 mg), ammonium formate (1.8 g, 28 mmol), methanol (25 mL) and water (10 mL) were mixed under nitrogen atmosphere. The mixture was refluxed for 2h. The catalyst was filtered off and ethyl acetate and sodium hydroxide (2 M) were added. The layers were separated and the aqueous phase was extracted three times with ethyl acetate. The organic layers were combined and dried (Na₂SO₄). The solvent was removed *in vacuo* to give 0.35 g of the title compound as an oil (75% yield): [α]_D²¹ -22° (c 1, MeOH); EIMS (70eV) *m/z* (relative intensity) 245 (5, M⁺).

Example 16**(*R*)-2-*N,N*-Dibenzylamino-8-(piperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

(*R*)-2-*N,N*-Dibenzylamino-8-amino-1,2,3,4-tetrahydronaphthalene (9.8 g, 39 mmol) and bis-(2-chloroethyl)amine hydrochloride (5.5 g, 32 mmol) was dissolved in n-butanol (80 mL). The reaction mixture was stirred at 100 °C and after 65 h the mixture was filtered and the solvent evaporated *in vacuo*. Purification on a silica gel column using chloroform/methanol/ concentrated ammonium hydroxide (95:5:0.5) as the eluent gave 6.0

g (51% yield) of the title compound as a viscous oil: $[\alpha]^{21}_{\text{D}} +72^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 411 (2, M^+).

Example 17

5 (R)-2-Amino-8-(piperazin-1-yl)-1,2,3,4-tetrahydronaphthalene

To a solution of (R)-2-*N,N*-dibenzylamino-8-(piperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (5.5 g, 13 mmol) in methanol (400 mL) were added ammonium formate (20 g, 0.32 mol) and palladium (10%) on activated carbon (1.9 g). The mixture was refluxed for 1 h and the palladium was then filtered off. The solvent was evaporated *in vacuo* and the residue was
10 partitioned between methylene chloride and a 2 M ammonium hydroxide solution. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol/concentrated ammonium hydroxide (80:20:2.5) as the eluent. Yield: 2.4 g (76%) of the title compound as an oil: $[\alpha]^{21}_{\text{D}} +9.9^{\circ}$ (*c* 1.0, chloroform); EIMS (70 eV)
15 *m/z* (relative intensity) 231 (24, M^+).

Example 18

tert-Butyl (R)-4-(7-Amino-5,6,7,8-tetrahydro-1-naphthyl)piperazine-1-carboxylate

To an ice-cooled solution of (R)-2-amino-8-(piperazin-1-yl)-1,2,3,4-tetrahydronaphthalene
20 (1.5 g, 6.5 mmol) and triethylamine (1.0 mL, 7.5 mmol) in methylene chloride (400 mL) was di-*tert*-butyl dicarbonate (1.5 mL, 6.5 mmol) in methylene chloride (50 mL) added dropwise. After the addition the reaction was allowed to stir at ambient temperature for 1 h and was then washed with a dilute aqueous sodium hydrogen carbonate solution. The methylene chloride phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* and the
25 crude product was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent to afford 1.0 g (45% yield) of the title compound as a colorless viscous oil: $[\alpha]^{21}_{\text{D}} +34^{\circ}$ (*c* 1.0, chloroform); EIMS (70 eV) *m/z* (relative intensity) 331 (100, M^+).

Example 19**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide**

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.41 mmol) and triethylamine (110 μ L, 0.82 mmol) in methylene chloride (25 mL) was added acetyl chloride (31 μ L, 0.43 mmol) in methylene chloride (10 mL). After the addition the reaction was allowed to reach room temperature and then washed with water. The phases were separated, the combined organic phases were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:4:0.5) as the eluent. Yield: 110 mg (90%) of the title compound as an oil. Crystallization from ethyl acetate/hexane gave 52 mg (44% yield) of white crystals: mp 152-154 °C; [α]_D²¹ +66° (c 0.13, chloroform); EIMS (70eV) *m/z* (relative intensity) 287 (9, M⁺).

Example 20**(R)-N-[8-(Piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide**

To an ice-cooled solution of *tert*-butyl (R)-4-(7-amino-5,6,7,8-tetrahydro-1-naphthyl)piperazine-1-carboxylate (120 mg, 0.36 mmol) and triethylamine (100 μ L, 0.72 mmol) in methylene chloride (30 mL) acetyl chloride (26 μ L, 0.36 mmol) in methylene chloride (5 mL) was added dropwise. After the addition the reaction was allowed to stir at ambient temperature for 20 min and was then washed with water. The methylene chloride phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* and the crude product was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent to afford 130 mg (92% yield) of a viscous oil: EIMS (70 eV) *m/z* (relative intensity) 373 (40, M⁺). This oil was dissolved in methylene chloride (25 mL), without further characterization and trifluoroacetic acid (1.0 mL) was added. The reaction was stirred for 7 h at ambient temperature, water was added and the mixture was cooled on an ice-bath. After alkalization with 2 M aqueous sodium hydroxide solution the mixture was extracted, twice, with methylene chloride. The combined organic phases were dried (Na₂SO₄), filtered and evaporated *in vacuo*. Purification on a silica gel column using

chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent gave 60 mg (61% yield from *tert*-butyl (*R*)-4-(7-amino-5,6,7,8-tetrahydro-1-naphthyl)piperazine-1-carboxylate) of the title compound as a viscous oil: $[\alpha]^{21}_{\text{D}} +31^{\circ}$ (*c* 0.50, chloroform); EIMS (70eV) *m/z* (relative intensity) 273 (100, M^+).

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Example 21

(*R*)-*N*-[8-(4-Ethylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide

To a mixture of (*R*)-*N*-[8-(piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide (100 mg, 0.37 mmol), potassium carbonate (76 mg, 0.54 mmol) and potassium iodide (15 mg, 0.10 mmol) in acetone (20 mL) was added ethyl bromide (56 μL , 0.74 mmol) added and the reaction mixture was vigorously stirred over night. The reaction was filtered and the solvent was evaporated *in vacuo*. The residue was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent. This gave 87 mg (78% yield) of the title compound as an oil which was crystallized from ethyl acetate/hexane. Yield: 55 mg (50%) as white crystals: mp 142-143 $^{\circ}\text{C}$; $[\alpha]^{21}_{\text{D}} +27^{\circ}$ (*c* 0.50, chloroform); EIMS (70 eV) *m/z* (relative intensity) 301 (100, M^+).

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Example 22

(*R*)-2-*N,N*-Dibenzylamino-8-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene

To a mixture of (*R*)-2-*N,N*-dibenzylamino-8-(piperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (200 mg, 0.49 mmol) and potassium carbonate (100 mg, 0.74 mmol) in acetone (15 mL) was added propyl iodide (72 μL , 0.74 mmol) and the reaction mixture was vigorously stirred overnight at 50 $^{\circ}\text{C}$. The reaction was filtered and the solvent was evaporated *in vacuo*. The residue was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:1) as the eluent. This gave 180 mg (81% yield) of the title compound as an oil: EIMS (70 eV) *m/z* (relative intensity) 453 (5, M^+).

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Example 23**(R)-2-Amino-8-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

To a solution of (R)-2-*N,N*-dibenzylamino-8-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (180 mg, 0.4 mmol) in methanol (15 mL) were added ammonium formate (0.60 g, 2.4 mmol) and palladium (10%) on activated carbon (60 mg). The mixture was refluxed for 2 h and the palladium was then filtered off. The solvent was evaporated *in vacuo* and the residue was partitioned between methylene chloride and a 2 M ammonium hydroxide solution. The organic phase was separated, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as an oil. Yield: 85 mg (78%); EIMS (70 eV) *m/z* (relative intensity) 273 (4, M⁺).

Example 24**(R)-N-[8-(4-Propylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide**

To an ice-cooled solution of (R)-2-amino-8-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (85 mg, 0.31 mmol) and triethylamine (38 µL, 0.37 mmol) in methylene chloride (15 mL) was added acetyl chloride (23 µL, 0.31 mmol) in methylene chloride (5 mL) dropwise. After the addition the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The methylene chloride phase was dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified on a silica gel column using chloroform/ethanol saturated with (NH₃) (100:3) as the eluent. This gave 91 mg (93% yield) of the title compound as an oil which was crystallized from ethyl acetate/hexane. Yield: 61 mg (62%) as white crystals: mp 139-140 °C; [α]_D²¹ +26° (c 0.50, chloroform); EIMS (70 eV) *m/z* (relative intensity) 315 (78, M⁺).

Example 25**(R)-2-*N,N*-Dibenzylamino-8-(4-butylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

To a mixture of (R)-2-*N,N*-dibenzylamino-8-(piperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (300 mg, 0.73 mmol), potassium carbonate (150 mg, 1.1 mmol) and potassium iodide (catalytic amount) in *N,N*-dimethylformamide (25 mL) was added butyl bromide (130 mg, 0.95 mmol) and the reaction mixture was vigorously stirred overnight at 60 °C. The

reaction was filtered and the solvent was evaporated *in vacuo*. The residue was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:1) as the eluent. This gave 300 mg (86% yield) of the title compound as an oil: $[\alpha]^{21}_{\text{D}} +68^{\circ}$ (*c* 0.72, chloroform); EIMS (70 eV) *m/z* (relative intensity) 467 (5, M⁺).

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Example 26

(*R*)-2-Amino-8-(4-butylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene

To a solution of (*R*)-2-*N,N*-dibenzylamino-8-(4-butylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (300 mg, 0.63 mmol) in methanol (20 mL) were added ammonium formate (0.95 g, 3.8 mmol) and palladium (10%) on activated carbon (90 mg). The mixture
10 was refluxed for 2 h and the palladium was then filtered off. The solvent was evaporated *in vacuo* and the residue was partitioned between methylene chloride and a 2 M ammonium hydroxide solution. The organic phase was separated, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as an oil. Yield: 100 mg (56%): $[\alpha]^{21}_{\text{D}} -$
15 4.6° (*c* 1.3, chloroform); EIMS (70 eV) *m/z* (relative intensity) 287 (10, M⁺).

Example 27

(*R*)-*N*-[8-(4-Butylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide

To an ice-cooled solution of (*R*)-2-amino-8-(4-butylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.35 mmol) and triethylamine (53 μ L, 0.53 mmol) in
20 methylene chloride (25 mL) was added dropwise acetyl chloride (25 μ L, 0.35 mmol) in methylene chloride (10 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The methylene chloride phase was dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified on a silica gel
25 column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent. This gave, after crystallization from diethyl ether, 100 mg (89% yield) of the title compound as white crystals: mp 118-120 °C; $[\alpha]^{21}_{\text{D}} +25^{\circ}$ (*c* 0.54, chloroform); EIMS (70 eV) *m/z* (relative intensity) 329 (41, M⁺).

Example 28**(R)-2-N,N-Dibenzylamino-8-(4-pentylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

To a mixture of (R)-2-N,N-dibenzylamino-8-(piperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (500 mg, 1.2 mmol), potassium carbonate (250 mg, 1.8 mmol) and potassium iodide (catalytic amount) in N,N-dimethylformamide (30 mL) was added pentyl bromide (220 mg, 1.5 mmol) and the reaction mixture was vigorously stirred overnight at 60 °C. The reaction was filtered and the solvent was evaporated *in vacuo*. The residue was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:1) as the eluent. This gave 460 mg (79% yield) of the title compound as an oil: $[\alpha]^{21}_{\text{D}} +55.4^{\circ}$ (c 1.1, chloroform); EIMS (70 eV) *m/z* (relative intensity) 481 (3, M⁺).

Example 29**(R)-2-Amino-8-(4-pentylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

To a solution of (R)-2-N,N-dibenzylamino-8-(4-pentylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (450 mg, 0.94 mmol) in methanol (20 mL) were added ammonium formate (1.4 g, 5.6 mmol) and palladium (10%) on activated carbon (0.14 g). The mixture was refluxed for 2 h and the palladium was then filtered off. The solvent was evaporated *in vacuo* and the residue was partitioned between methylene chloride and a 2 M ammonium hydroxide solution. The organic phase was separated, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as an oil. Yield: 180 mg (64%): $[\alpha]^{21}_{\text{D}} -3.7^{\circ}$ (c 0.57, chloroform); EIMS (70 eV) *m/z* (relative intensity) 301 (47, M⁺).

Example 30**(R)-N-[8-(4-Pentylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide**

To an ice-cooled solution of (R)-2-amino-8-(4-pentylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (170 mg, 0.57 mmol) and triethylamine (86 μ L, 0.86 mmol) in methylene chloride (30 mL) was added dropwise acetyl chloride (41 μ L, 0.57 mmol) in methylene chloride (10 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The methylene chloride phase was dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue crystallized from diethyl ether/hexane. This gave 120

mg (62% yield) of the title compound as white crystals: mp 119-120 °C; $[\alpha]^{21}_{\text{D}} +25^{\circ}$ (c 0.97, chloroform); EIMS (70 eV) m/z (relative intensity) 343 (49, M^+).

Example 31

(*R*)-2-*N,N*-Dibenzylamino-8-(4-hexylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene

To a mixture of (*R*)-2-*N,N*-dibenzylamino-8-(piperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (440 mg, 1.1 mmol), potassium carbonate (220 mg, 1.8 mmol) and potassium iodide (catalytic amount) in *N,N*-dimethylformamide (25 mL) was added hexyl bromide (320 μg , 2.3 mmol) and the reaction mixture was vigorously stirred overnight at 60 °C. The reaction was filtered and the solvent was evaporated *in vacuo*. The residue was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:1) as the eluent. This gave 460 mg (79% yield) of the title compound as an oil: $[\alpha]^{21}_{\text{D}} +37^{\circ}$ (c 1.2, chloroform); EIMS (70 eV) m/z (relative intensity) 495 (3, M^+)

Example 32

(*R*)-2-Amino-8-(4-hexylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene

To a solution of (*R*)-2-*N,N*-dibenzylamino-8-(4-hexylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (300 mg, 0.60 mmol) in methanol (30 mL) were added ammonium formate (0.90 g, 3.6 mmol) and palladium (10%) on activated carbon (90 mg). The mixture was refluxed for 2 h and the palladium was then filtered off. The solvent was evaporated *in vacuo* and the residue was partitioned between methylene chloride and a 2 M ammonium hydroxide solution. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as an oil. Yield: 130 mg (68%): $[\alpha]^{21}_{\text{D}} -2.3^{\circ}$ (c 1.0, chloroform); EIMS (70 eV) m/z (relative intensity) 315 (91, M^+).

Example 33

(*R*)-*N*-[8-(4-Hexylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide

To an ice-cooled solution of (*R*)-2-amino-8-(4-hexylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (97 mg, 0.31 mmol) and triethylamine (51 μL , 0.37 mmol) in methylene chloride (15 mL) was added dropwise acetyl chloride (23 μL , 0.32 mmol) in

methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The methylene chloride phase was dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent. This gave after crystallization from diethyl ether/hexane 92 mg (83% yield) of the title compound as white crystals: mp 117-118 °C; [α]²¹_D +19° (c 1.0, chloroform); EIMS (70 eV) *m/z* (relative intensity) 357 (43, M⁺).

Example 34

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]trifluoroacetamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.49 mmol), pyridine (100 μ L, 1.2 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol) in methylene chloride (10 mL) was added dropwise trifluoroacetic anhydride (72 μ L, 0.51 mmol). After the addition the reaction was allowed to stir at ambient temperature for 1 h and was then washed with water. The methylene chloride phase was dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified on a silica gel column using ethyl acetate/methanol/concentrated ammonium hydroxide (96:4:0.5) as the eluent. This gave after crystalization from diethyl ether/hexane 41 mg (24% yield) of the title compound as white crystals: mp 158-159 °C; [α]²¹_D +39° (c 0.25, chloroform); EIMS (70 eV) *m/z* (relative intensity) 341 (82, M⁺).

Example 35

(R)-N-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]methanesulfonamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.49 mmol) and triethylamine (0.50 mL, 3.6 mmol) in pyridine (15 mL) was added dropwise methanesulfonyl chloride (62 μ L, 0.54 mmol). After the addition the reaction was allowed to stir at ambient temperature for 1 h. The solvent was evaporated *in vacuo* and the residue was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent. This gave, after crystalization from diethyl ether, 100 mg (63% yield) of the title compound as

white crystals: mp 135-137 °C; $[\alpha]^{21}_{\text{D}} +22^{\circ}$ (c 0.50, chloroform); EIMS (70 eV) m/z (relative intensity) 323 (59, M^+).

Example 36

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]cyclohexanecarboxamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.46 mmol) and triethylamine (92 μL , 0.66 mmol) in methylene chloride (20 mL) was added dropwise cyclohexanecarbonyl chloride (67 μL , 0.46 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient temperature for 10 min and then washed with dilute aqueous sodium hydrogen carbonate. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated *in vacuo* and the residue was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. This gave 71 mg (45% yield) of the title compound as white crystals: mp 183-184 °C; $[\alpha]^{21}_{\text{D}} +12^{\circ}$ (c 1.0, chloroform); EIMS (70 eV) m/z (relative intensity) 355 (56, M^+).

Example 37

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]butanamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (300 mg, 1.2 mmol) and triethylamine (260 μL , 1.8 mmol) in methylene chloride (50 mL) was added dropwise butyryl chloride (140 μL , 1.3 mmol) in methylene chloride (10 mL). After the addition the reaction was allowed to stir at ambient temperature for 1 h and then washed with a dilute aqueous sodium hydrogen carbonate solution. The phases were separated and the combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/methanol/ concentrated ammonium hydroxide (95:4:0.5) as the eluent. Yield: 330 mg (86%) of the title compound as white crystals: mp 131-132 °C; $[\alpha]^{21}_{\text{D}} +24^{\circ}$ (c 0.50, chloroform); EIMS (70eV) m/z (relative intensity) 315 (39, M^+).

Example 38**(R)-2-N-Butylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

To a solution of (R)-N-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]butanamide (290 mg, 0.92 mmol) in anhydrous diethyl ether (35 mL) was added lithium aluminium hydride (100 mg, 2.8 mmol). The reaction mixture was heated at reflux for 7 h, then cooled and quenched by the addition of water (100 μ L), 15% aqueous sodium hydroxide (100 μ L) and again water (530 μ L). The mixture was filtered, dried (Na_2SO_4) and evaporated *in vacuo*. Purification on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent gave 170 mg (63% yield) of the title compound as a viscous oil. $[\alpha]_D^{21} +3.1^\circ$ (c 1.0, chloroform); EIMS (70 eV) m/z (relative intensity) 301 (52, M^+). The oxalate salt was precipitated out of diethyl ether from 70 mg of the base. The crude salt was recrystallized from absolute ethanol and 77 mg (69% yield) of white crystals were isolated: mp 167-168°C.

Example 39**(R)-N-Butyl-N-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide**

To an ice-cooled solution of (R)-2-N-butylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (91 mg, 0.30 mmol) and triethylamine (50 μ L, 0.36 mmol) in methylene chloride (15 mL) was added dropwise acetyl chloride (23 μ L, 0.36 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The methylene chloride phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent gave 99 mg (96% yield) of the title compound as a viscous oil. $[\alpha]_D^{21} +14^\circ$ (c 1.0, chloroform); EIMS (70 eV) m/z (relative intensity) 343 (30, M^+).

The oxalate salt was precipitated out of diethyl ether and the crude salt was recrystallized from absolute ethanol/diethyl ether and 97 mg (73% yield) of white crystals were isolated: mp 153-154 °C.

Example 40**(R)-2-N-Methylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

To a solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (250 mg, 1.0 mmol) and triethylamine (210 μ L, 1.5 mmol) in anhydrous 1,4-dioxane was added dropwise ethyl chloroformate (110 μ L, 1.2 mmol) and the reaction was stirred for 15 min at room temperature. The slightly yellow, cloudy solution was evaporated *in vacuo* and the residue was partitioned between chloroform and water. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude oily product which was dissolved in diethyl ether (30 mL) and a small amount of tetrahydrofuran (8.0 mL). Lithium aluminium hydride (230 mg, 6.3 mmol) was added and the reaction mixture was heated at reflux for 20 h, cooled and then quenched by the addition of water (240 μ L), 15% aqueous sodium hydroxide (240 μ L) and again water (720 μ L). The mixture was filtered, dried (Na_2SO_4) and evaporated *in vacuo*. Purification on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent gave 120 mg (47% yield) of the title compound as a viscous oil: $[\alpha]^{21}_{\text{D}} +20^\circ$ (c 1.0, chloroform); EIMS (70 eV) m/z (relative intensity) 259 (64, M^+).

Example 41**(R)-N-Methyl-N-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]acetamide**

To an ice-cooled solution of (R)-2-N-methylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (85 mg, 0.33 mmol) and triethylamine (55 μ L, 0.4 mmol) in methylene chloride (20 mL) was added dropwise acetyl chloride (25 μ L, 0.35 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and then washed with water. The phases were separated and the combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent. Yield: 61 mg (66%) of the title compound as an oil: $[\alpha]^{21}_{\text{D}} +54^\circ$ (c 1.0, chloroform); EIMS (70 eV) m/z (relative intensity) 301 (18, M^+).

Example 42

(*R*)-2-*N*-Isopropylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene
(*R*)-2-Amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (200 mg, 0.81
mmol) and acetone (0.20 mL, 2.7 mmol) was dissolved in methanol (5.0 mL). The pH was
5 adjusted to 6 with acetic acid and sodium cyanoborohydride (66 mg, 1.1 mmol) was added.
After 3 h at ambient temperature the solvent was evaporated *in vacuo* and the residue was
partitioned between chloroform and water. The water phase was alkalized with 2 M
aqueous sodium hydroxide solution and the phases were separated. The organic phase was
dried (Na₂SO₄), filtered and evaporated *in vacuo*. Chromatography on silica (eluent:
10 chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5)) gave 110 mg (47%
yield) of the title compound as a viscous clear oil: [α]_D²¹ +3° (c 1.0, chloroform); EIMS
(70eV) *m/z* (relative intensity) 287 (23, M⁺).

Example 43

15 (*R*)-*N*-Isopropyl-*N*-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-
naphthyl]acetamide

To an ice-cooled solution of (*R*)-2-*N*-isopropylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-
tetrahydronaphthalene (110 mg, 0.38 mmol) and triethylamine (63 μ L, 0.46 mmol) in
methylene chloride (20 mL) was added dropwise acetyl chloride (31 μ L, 0.40 mmol) in
20 methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient
temperature for 15 min and then washed with water. The phases were separated and the
combined organic phases were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a
crude product which was purified on a silica gel column using
chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent. Yield:
25 120 mg (92%) of the title compound as an oil. [α]_D²¹ -24° (c 1.0, chloroform); EIMS
(70eV) *m/z* (relative intensity) 329 (31, M⁺). The oxalate salt was precipitated out of
diethyl ether and the crude salt was recrystallized from absolute ethanol/diethyl ether and
85 mg (48% yield) of white crystals were isolated: mp 181-183 °C.

Example 44**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-1,1'-biphenyl-4-carboxamide**

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.41 mmol) and triethylamine (62 μ L, 0.45 mmol) in methylene chloride (20 mL) was added dropwise 4-biphenylcarbonyl chloride (89 mg, 0.41 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and then washed with water. The phases were separated and the combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:2.5) as the eluent. Yield: 100 mg (59%) of the title compound as white crystals: mp 232-233 $^\circ\text{C}$; EIMS (70eV) *m/z* (relative intensity) 425 (11, M^+).

Example 45**(R)-8-(4-Methylpiperazin-1-yl)-2-N-(4-phenyl)benzylamino-1,2,3,4-tetrahydronaphthalene**

To a solution of (R)-N-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-1,1'-biphenyl-4-carboxamide (210 mg, 0.49 mmol) in anhydrous diethyl ether (75 mL) and tetrahydrofuran (8 mL) was added lithium aluminium hydride (95 mg, 2.5 mmol). The reaction mixture was heated at reflux for 4 h, cooled and then quenched by the addition of water (95 μ L), 15% aqueous sodium hydroxide (95 μ L) and again water (290 μ L). The mixture was filtered, dried (Na_2SO_4) and evaporated *in vacuo*. Purification on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:4:0.5) as the eluent gave 180 mg (87% yield) of the title compound as a viscous oil: $[\alpha]_D^{21} +15^\circ$ (c 1.0, chloroform); EIMS (70 eV) *m/z* (relative intensity) 411 (7, M^+).

Example 46**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-2-phenylthiazole-4-carboxamide**

To a solution of 4-carboxy-2-phenylthiazole (88 mg, 0.43 mmol) in anhydrous *N,N*-dimethylformamide (25 mL) was added 1,1'-carbonyldiimidazole (73 mg, 0.45 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 30 min), the reaction was cooled to room temperature and a solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.41 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added. The reaction was allowed to stir at ambient temperature for 17 h and the solvent was evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent gave 99 mg (56% yield) of the title compound as white crystals: mp 175-176 °C; [α]_D²¹ -85° (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 432 (6, M⁺).

Example 47**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-2-(4-pyridyl)thiazole-4-carboxamide**

To a solution of 4-carboxy-2-(4-pyridyl)thiazole (89 mg, 0.43 mmol) in anhydrous *N,N*-dimethylformamide (25 mL) was added 1,1'-carbonyldiimidazole (73 mg, 0.45 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 30 min), the reaction was cooled to room temperature and a solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.41 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added. The reaction was allowed to stir at ambient temperature for 17 h and the solvent was evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent gave 110 mg (61% yield) of the title compound as white crystals: mp 187-188 °C; [α]_D²¹ -82° (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 433 (2, M⁺).

Example 48**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]benzamide**

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (210 mg, 0.86 mmol) and triethylamine (180 μ L, 1.28 mmol) in methylene chloride (30 mL) was added dropwise benzoyl chloride (130 mg, 0.90 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and then washed with water. The phases were separated and the combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. Yield: 250 mg (84%) of the title compound as white crystals: mp 195-196 $^{\circ}\text{C}$; $[\alpha]^{21}_{\text{D}} -31^{\circ}$ (c 1.0, CHCl_3); EIMS (70eV) *m/z* (relative intensity) 349 (53, M^+).

Example 49**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-methoxybenzamide**

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (130 mg, 0.53 mmol) and triethylamine (110 μ L, 0.80 mmol) in methylene chloride (30 mL) was added dropwise 4-methoxybenzoyl chloride (95 mg, 0.56 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and then washed with water. The phases were separated and the combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. Yield: 143 mg (71%) of the title compound as white crystals: mp 186-187 $^{\circ}\text{C}$; $[\alpha]^{21}_{\text{D}} -52^{\circ}$ (c 0.50, CHCl_3); EIMS (70eV) *m/z* (relative intensity) 379 (23, M^+).

Example 50

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-cyanobenzamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (130 mg, 0.53 mmol) and triethylamine (110 μ L, 0.80 mmol) in methylene chloride (25 mL) was added dropwise 4-cyanobenzoyl chloride (92 mg, 0.56 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and then washed with water. The phases were separated and the combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:4) as the eluent. Yield: 120 mg (61%) of the title compound as white crystals: mp 184-186 $^{\circ}\text{C}$; $[\alpha]_D^{21}$ -47 $^{\circ}$ (c 1.0, CHCl_3); EIMS (70eV) *m/z* (relative intensity) 374 (54, M^+).

Example 51

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylsulfonyloxybenzamide

4-Carboxyphenyl trifluoromethanesulfonate (0.40 g, 1.5 mmol; described in: Looker, J. H.; Hayes, C. H.; Thatcher, D. N. *J. Am. Chem. Soc.* **1957**, 79, 741-4) was dissolved in thionyl chloride (10 mL) and heated at 40 $^{\circ}\text{C}$ for 45 min. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. The crude acid chloride (280 mg, 0.96 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.46 mmol) and triethylamine (96 μ L, 0.69 mmol) in methylene chloride (20 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and then washed with water. The phases were separated and the combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. Yield: 100 mg (44%) of the title compound as white crystals: mp 178-180 $^{\circ}\text{C}$; $[\alpha]_D^{21}$ -31 $^{\circ}$ (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 497 (17, M^+).

Example 52**(R)-N-[8-(4-*tert*-Butyloxycarbonylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide**

5 To a solution of 4-morpholinobenzoic acid (0.59 g, 2.8 mmol; described in: Degutis, J.; Rasteikiene, L.; Degutiene, A. *Zh. Org. Khim.* **1978**, *14*(10), 2060-2064) in anhydrous *N,N*-dimethylformamide (30 mL) was added 1,1'-carbonyldiimidazole (0.48 g, 3.0 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 30 min), the reaction was cooled to room temperature and a solution of *tert*-butyl (R)-4-(7-amino-5,6,7,8-tetrahydro-1-naphthyl)piperazine-1-carboxylate (0.90 g, 2.7 mmol) in
10 anhydrous *N,N*-dimethylformamide (15 mL) was added. The reaction was allowed to stir at ambient temperature for 24 h and the solvent was evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:2) as the eluent gave 1.5 g (84% yield) of the title compound as a dark-red viscous oil: $[\alpha]^{21}_D$ -45° (c 0.50, chloroform); EIMS (70eV) *m/z* (relative intensity) 520 (5, M⁺).
15

Example 53**(R)-N-[8-(Piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide**

To an ice-cooled solution of (R)-N-[8-(4-*tert*-butyloxycarbonylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinophenylcarboxamide (1.0 g, 2 mmol) in methylene
20 chloride (100 mL) was added trifluoroacetic acid (3 mL). The reaction was stirred at ambient temperature for 7 h. The solvent was evaporated *in vacuo* and the residue was dissolved in water (20 mL), alkalized with a 2 M aqueous sodium hydroxide solution and extracted, twice, with methylene chloride. The phases were separated, the combined organic
25 phases were dried (Na₂SO₄), filtered and evaporated *in vacuo*. Purification on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent gave 580 mg (70% yield) of the title compound as white crystals: mp 202-203 °C; $[\alpha]^{21}_D$ -56° (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 420 (5, M⁺).

Example 54**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide**

To a solution of 4-morpholinobenzoic acid (0.89 g, 4.3 mmol; described in: Degutis, J.; Rasteikiene, L.; Degutiene, A. *Zh. Org. Khim.* **1978**, *14*(10), 2060-2064) in anhydrous *N,N*-dimethylformamide (30 mL) was added 1,1'-carbonyldiimidazole (0.73 g, 4.3 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 30 min), the reaction was cooled to room temperature and a solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (1.0 g, 4.1 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added. The reaction was allowed to stir at ambient temperature for 24 h and the solvent was evaporated *in vacuo*. Purification on a silica gel column using chloroform/methanol/ concentrated ammonium hydroxide (95:5:0.5) as the eluent gave 1.5 g (85% yield) of the title compound as white crystals: mp 230-231 °C; $[\alpha]^{21}_{\text{D}} -49^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 434 (10, M^{+}).

Example 55**(S)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide**

The title compound was synthesized according to the procedure of Example 54 using the (*S*)-form: mp 228-230 °C; $[\alpha]^{21}_{\text{D}} +35^{\circ}$ (*c* 1, MeOH); EIMS (70eV) *m/z* (relative intensity) 434 (1, M^{+}).

Example 56**R)-N-[8-(4-Ethylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide**

To a solution of (*R*)-N-8-(piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (90 mg, 0.21 mmol) in acetone (20 mL) were added potassium carbonate (44 mg, 0.32 mmol) and iodoethane (26 μL , 0.32 mmol) and the reaction was stirred for 48 h at ambient temperature. The reaction mixture was filtered and the solvent evaporated *in vacuo*. The residue was partitioned between methylene chloride and water,

the phases were separated, and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent gave 63 mg (66% yield) of the title compound as white crystals: mp: 204-206 °C; [α]²¹_D -67° (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 448 (21, M⁺).

Example 57

(R)-N-[8-(4-Propylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide

To a solution of (R)-N-8-(piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (120 mg, 0.29 mmol) in acetone (20 mL) were added potassium carbonate (59 mg, 0.43 mmol) and 1-iodopropan (42 μ L, 0.43 mmol) and the reaction was stirred for 4 days at ambient temperature. The reaction mixture was filtered and the solvent evaporated *in vacuo*. The residue was partitioned between methylene chloride and water, the phases separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:4) as the eluent gave 58 mg (44% yield) of the title compound as a amorphous solid. Crystallization from ethyl acetate/diethyl ether gave 11 mg (8%) of white crystals: mp 183-185 °C; [α]²¹_D -60° (c 0.50, chloroform); EIMS (70eV) *m/z* (relative intensity) 462 (25, M⁺).

Example 58

(R)-8-(4-Methylpiperazin-1-yl)-2-[N-(4-morpholino)benzylamino]-1,2,3,4-tetrahydronaphthalene

To a solution of (R)-N-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide (200 mg, 0.46 mmol) in anhydrous tetrahydrofuran (25 mL) was added lithium aluminium hydride (200 mg, 5.3 mmol). The reaction mixture was heated at reflux for 15 h, then cooled and quenched by the addition of water (200 μ L), 15% aqueous sodium hydroxide (200 μ L) and again water (600 μ L). The mixture was filtered, dried (Na₂SO₄) and evaporated *in vacuo*. Purification on a silica gel column using

chloroform/methanol/concentrated ammonium hydroxide (95:5:0.5) as the eluent gave 61 mg (32% yield) of the title compound as white crystals: $[\alpha]^{21}_{\text{D}} +19^{\circ}$ (c 1.0, chloroform); EIMS (70 eV) m/z (relative intensity) 420 (8, M^+).

5 **Example 59**

3-Methyl-4-morpholinobenzonitrile

To a solution of 4-bromo-3-methylbenzonitrile (11 g, 56 mmol) and potassium fluoride (3.3 g, 56 mmol) in anhydrous *N,N*-dimethylformamide (150 mL) was added morpholine (15 g, 170 mmol) and the reaction was heated at 145 °C for 4 days. The solvent was evaporated *in vacuo* and the residue was partitioned between diethyl ether and water. The phases were
10 separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification on a silica gel column using toluene followed by chloroform as eluents gave 1.3 g (11% yield) of the title compound as white crystals: mp 85-86 °C; EIMS (70 eV) m/z (relative intensity) 202 (71, M^+).

15

Example 60

3-Methyl-4-morpholinobenzoic acid

To a solution of 3-methyl-4-morpholinobenzonitrile (1.0 g, 4.9 mmol) in glacial acetic acid (10 mL) was added a 20% aqueous hydrochloric acid solution (60 mL) and the reaction was
20 heated at reflux for 35 h. The acetic acid was evaporated *in vacuo* and the remaining water solution was alkalized with 2 M aqueous sodium hydroxide solution to pH 8. The solution was washed, twice, with chloroform and the water phase was adjusted to pH 4 with a 2 M aqueous hydrochloric acid solution. The product was filtered off and dried *in vacuo* to afford 1.0 g (91% yield) of the title compound as white crystals: mp 220-221 °C; EIMS
25 (70 eV) m/z (relative intensity) 221 (100, M^+).

Example 61**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-methyl-4-morpholinobenzamide**

To a solution of 3-methyl-4-morpholinobenzoic acid (110 mg, 0.51 mmol) in anhydrous *N,N*-dimethylformamide (10 mL) was added 1,1'-carbonyldiimidazole (87 mg, 0.54 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 30 min), the reaction was cooled to room temperature and a solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.49 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added. The reaction was allowed to stir at ambient temperature for 15 h and the solvent was evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:2) as the eluent gave 110 mg (50% yield) of the title compound as white crystals: mp 172-175 °C; [α]_D²¹ -47° (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 448 (5, M⁺).

Example 62**(R)-N-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-piperidinobenzamide**

To a solution of 4-piperidinobenzoic acid (88 mg, 0.43 mmol; described in: Weringa, W. D.; Janssen, M. J. *Recl. Trav. Chim. Pays-Bas* **1968**, 87(12), 1372-1380) in anhydrous *N,N*-dimethylformamide (5 mL) was added 1,1'-carbonyldiimidazole (73 mg, 0.45 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 30 min), the reaction was cooled to room temperature and a solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.41 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added. The reaction was allowed to stir at ambient temperature for 17 h and the solvent was evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:2) as the eluent gave 75 mg (42% yield) of the title compound as white crystals: mp 196-198 °C; [α]_D²¹ -63° (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 432 (2, M⁺).

Example 63**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-cyclohexylbenzamide**

4-Cyclohexylbenzoic acid (0.50 g, 2.4 mmol) was dissolved in thionyl chloride (20 mL) and heated at reflux for 30 min. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (96 mg, 0.43 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.41 mmol) and triethylamine (62 μ L, 0.45 mmol) in methylene chloride (20 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and then washed with water. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/methanol/ concentrated ammonium hydroxide (95:5:0.5) as the eluent. Yield: 150 mg (85%) of the title compound as white crystals: mp 224-226 °C; [α]_D²¹ -43° (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 431 (2, M⁺).

Example 64**(S)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-N,N-diethylaminobenzamide**

4-(diethylamino)benzoic acid (94 mg, 0.5 mmol) and 1,1-carbonyldiimidazole (86 mg, 0.5 mmol) were dissolved in *N,N*-dimethylformamide (4 mL) under nitrogen atmosphere and stirred at 70 °C for 30 minutes. The reaction mixture was allowed to attain room temperature before (S)-2-Amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (0.1 g, 0.4 mmol), dissolved in *N,N*-dimethylformamide (4 mL), was added. The mixture was stirred at room temperature for 10 days before it was diluted with ethyl acetate, washed with 2 M ammonia and dried (MgSO₄). The solvent was removed *in vacuo* to give a residue which was purified by flash chromatography on silica gel with methylene chloride/ethyl acetate 20:1 (containing 0.5% of ammonia) as eluent. yield 40 mg (23%): mp

168-170 °C (dec); $[\alpha]^{21}_{\text{D}} +25^{\circ}$ (c 0.25, MeOH); EIMS (70eV) m/z (relative intensity) 420 (13, M^+).

Example 65

5 **(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylbenzamide**

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.44 mmol) and triethylamine (91 μL , 0.66 mmol) in methylene chloride (20 mL) was added dropwise 4-(trifluoromethyl)benzoyl chloride (96
10 mg, 0.46 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and was then washed with diluted aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:2) as the eluent.
15 Yield: 150 mg (81%) of the title compound as white crystals: mp 203-204 °C; $[\alpha]^{21}_{\text{D}} -20^{\circ}$ (c 1.0, chloroform); EIMS (70eV) m/z (relative intensity) 417 (10, M^+).

Example 66

20 **(S)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylbenzamide**

The title compound was synthesized according to the procedure of Example 65 using the (S)-form: mp 202-204°C; $[\alpha]^{21}_{\text{D}} -13^{\circ}$ (c 1, MeOH); EIMS (70eV) m/z (relative intensity) 417 (5, M^+).

Example 67

25 **(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-methylsulfonyloxybenzamide**

A suspension of 4-methylsulfonyloxybenzoic acid (0.60 g, 2.8 mmol; described in: Looker, J. H.; Hayes, C. H.; Thatcher, D. N. *J. Am. Chem. Soc.* **1957**, 79, 741-4) in thionyl chloride
30 (15 mL) was heated at reflux for 30 min (the mixture became homogeneous). The excess of

thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (110 mg, 0.47 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.45 mmol) and triethylamine (94 μ L, 0.68 mmol) in methylene chloride (20 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. Yield: 160 mg (78%) of the title compound as white crystals: mp 199-200 $^\circ\text{C}$; $[\alpha]_D^{21} -20^\circ$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 443 (3, M^+).

Example 68

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-hydroxybenzamide A suspension of sodium 4-acetoxybenzoate (1.0 g, 5.4 mmol) in thionyl chloride (15 mL) was heated at reflux for 1 h (the mixture became homogeneous). The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (150 mg, 0.77 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (180 mg, 0.73 mmol) and triethylamine (150 μ L, 1.1 mmol) in methylene chloride (20 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and was then washed with diluted aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was dissolved in 99.5% ethanol (15 mL) and concentrated hydrochloric acid (5 mL) was added. After 17 h, the pH was adjusted to 8 and the solvent evaporated *in vacuo*. The residue was partitioned between water and chloroform. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:4) as the eluent.

Yield: 70 mg (26%) of the title compound as an oil: $[\alpha]^{21}_{\text{D}} -17^{\circ}$ (*c* 0.50, chloroform); EIMS (70eV) *m/z* (relative intensity) 365 (24, M^+).

Example 69

5 **(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-ethylbenzamide**

To an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.46 mmol) and triethylamine (95 μL , 0.68 mmol) in methylene chloride (20 mL) was added dropwise 4-ethylbenzoyl chloride (81 mg, 0.48 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at
10 ambient temperature for 15 min and then washed with water. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:4) as the eluent. Yield: 120 mg (66%) of the title compound as white crystals:
15 mp 177-178 $^{\circ}\text{C}$; $[\alpha]^{21}_{\text{D}} -43^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 377 (27, M^+).

Example 70

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-butoxybenzamide

To an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.41 mmol) and triethylamine (95 μL , 0.69 mmol) in methylene chloride (20 mL) was added dropwise 4-butoxybenzoyl chloride (103 mg, 0.48 mmol) in methylene chloride (5 mL). After the addition the reaction was allowed to stir at
20 ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered
25 and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:2) as the eluent. Yield: 150 mg (75%) of the title compound as white crystals: mp 190-191 $^{\circ}\text{C}$; $[\alpha]^{21}_{\text{D}} -49^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 421 (0.6, M^+).

Example 71

(S)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-butoxybenzamide

The title compound was synthesized according to the procedure of Example 70 using the (S)-form: mp 190-192 °C; $[\alpha]^{21}_{\text{D}} +8^{\circ}$ (c 1, MeOH); EIMS (70eV) *m/z* (relative intensity) 421 (1, M⁺).

Example 72

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-fluorobenzamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (130 mg, 0.53 mmol) and triethylamine (110 μL, 0.79 mmol) in methylene chloride (25 mL) was added dropwise 4-fluorobenzoyl chloride (89 mg, 0.56 mmol) in methylene chloride (5 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with diluted aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent. Yield: 130 mg (65%) of the title compound as white crystals: mp 189-190 °C; $[\alpha]^{21}_{\text{D}} -30^{\circ}$ (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 367 (11, M⁺).

Example 73

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-bromobenzamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (130 mg, 0.53 mmol) and triethylamine (110 μL, 0.79 mmol) in methylene chloride (25 mL) was added dropwise 4-bromobenzoyl chloride (122 mg, 0.56 mmol) in methylene chloride (5 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:4) as the eluent. Yield: 120 mg (51%) of

the title compound as white crystals: mp 200-201 °C; $[\alpha]_D^{21} -32^\circ$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 427 and 429 (3, M^+).

Example 74

5 **(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-chlorobenzamide**
To an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.45 mmol) and triethylamine (93 μ L, 0.67 mmol) in methylene chloride (25 mL) was added dropwise 4-chlorobenzoyl chloride (83 mg, 0.47 mmol) in methylene chloride (5 mL). After the addition, the reaction was allowed to stir at
10 ambient temperature for 15 min and was then washed with diluted aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. Yield: 97 mg (56%) of the title compound as white crystals: mp 204-205 °C; $[\alpha]_D^{21} -46^\circ$
15 (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 383 (19, M^+).

Example 75

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-benzylbenzamide
4-Benzylbenzoic acid (0.50 g, 2.4 mmol) was dissolved in thionyl chloride (10 mL) and
20 heated at reflux for 20 min. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (100 mg, 0.46 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.44 mmol) and triethylamine (90 μ L, 0.65 mmol) in
25 methylene chloride (25 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. Yield: 130 mg (62%) of

the title compound as white crystals: mp 191-192 °C; $[\alpha]^{21}_{\text{D}} -39^{\circ}$ (c 1.0, chloroform); EIMS (70eV) m/z (relative intensity) 439 (28, M^+).

Example 76

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-benzoylbenzamide

4-Benzoylbenzoic acid (0.50 g, 2.2 mmol) was dissolved in thionyl chloride (15 mL) and heated at reflux for 15 min. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (150 mg, 0.60 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (140 mg, 0.57 mmol) and triethylamine (120 μL , 0.86 mmol) in methylene chloride (30 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. Yield: 120 mg (48%) of the title compound as white crystals: mp 194-195°C; $[\alpha]^{21}_{\text{D}} -51^{\circ}$ (c 1.0, chloroform); EIMS (70eV) m/z (relative intensity) 453 (2, M^+).

Example 77

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(trifluoroacetyl)benzamide

4-(Trifluoroacetyl)benzoic acid (0.50 g, 2.4 mmol) was dissolved in thionyl chloride (15 mL) and heated at reflux for 20 min. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (97 mg, 0.43 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.41 mmol) and triethylamine (85 μL , 0.61 mmol) in methylene chloride (35 mL). After the addition, the reaction was allowed to stir at

ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent. Yield: 98 mg (54%) of the title compound as slightly yellow crystals: mp 91-93 °C; [α]_D²¹ -47° (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 453 (27, M⁺).

Example 78

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(1H-pyrrol-1-yl)benzamide

To a solution of 4-(1H-pyrrol-1-yl)benzoic acid (96 mg, 0.51 mmol) in anhydrous *N,N*-dimethylformamide (25 mL) was added 1,1'-carbonyldiimidazole (87 mg, 0.54 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 30 min), the reaction was cooled to room temperature and a solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.49 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added. The reaction was allowed to stir at ambient temperature for 17 h and the solvent was evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent gave 128 mg (62% yield) of the title compound as white crystals: mp 245-247 °C; [α]_D²¹ -69° (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 414 (15, M⁺).

Example 79

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(*N,N*-dipropylaminosulphonyl)benzamide

To a solution of 4-(*N,N*-dipropylaminosulphonyl)benzoic acid (120 mg, 0.43 mmol) in anhydrous *N,N*-dimethylformamide (25 mL) was added 1,1'-carbonyldiimidazole (73 mg, 0.45 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 30 min), the reaction was cooled to room temperature and a solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.41 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added. The reaction was allowed to stir at

ambient temperature for 24 h and the solvent was evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent gave 58 mg (27% yield) of the title compound as a viscous oil: $[\alpha]^{21}_{\text{D}} -37^{\circ}$ (c 0.50, chloroform); EIMS (70eV) *m/z* (relative intensity) 512 (11, M⁺).

5

Example 80

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]phenylacetamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.43 mmol) and triethylamine (88 μ L, 0.64 mmol) in
10 methylene chloride (20 mL) was added dropwise phenylacetyl chloride (70 mg, 0.45 mmol) in methylene chloride (5 mL). After the addition, the reaction was allowed to stir at ambient temperature for 10 min and then washed with water. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with
15 NH₃ (100:3) as the eluent. Yield: 95 mg (61%) of the title compound as white crystals: mp 151-152 $^{\circ}$ C; $[\alpha]^{21}_{\text{D}} -4.3^{\circ}$ (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 363 (21, M⁺).

Example 81

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-phenylpropanamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (99 mg, 0.40 mmol) and triethylamine (83 μ L, 0.42 mmol) in methylene chloride (20 mL) was added dropwise 3-phenylpropionyl chloride (72 mg, 0.42
25 mmol) in methylene chloride (5 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and then washed with water. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:4) as the eluent. Yield: 120 mg (61%) of the title compound as white crystals:

mp 184-186 °C; $[\alpha]^{21}_{\text{D}} +6.5^\circ$ (c 1.0, chloroform); EIMS (70eV) m/z (relative intensity) 374 (54, M^+).

Example 82

5 **(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-phenylbutanamide**

4-Phenylbutyric acid (1.0 g, 6.1 mmol) was dissolved in thionyl chloride (15 mL) and heated at reflux for 1 h. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (86
10 mg, 0.47 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.45 mmol) and triethylamine (93 μL , 0.68 mmol) in methylene chloride (15 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The phases were separated and the organic phase was dried
15 (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:4) as the eluent. Yield: 150 mg (82%) of the title compound as white crystals: mp 137-139 °C; $[\alpha]^{21}_{\text{D}} +8.4^\circ$ (c 0.50, chloroform); EIMS (70eV) m/z (relative intensity) 391 (23, M^+).

20 **Example 83**

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-5-phenylpentanamide

5-Phenylvaleric acid (1.0 g, 5.6 mmol) was dissolved in thionyl chloride (15 mL) and heated at reflux for 1 h. The excess of thionyl chloride was evaporated *in vacuo*, the residue was
25 treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (93 mg, 0.47 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.45 mmol) and triethylamine (93 μL , 0.68 mmol) in methylene chloride (15 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and
30 was then washed with water. The phases were separated and the organic phase was dried

(Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:4) as the eluent. Yield: 120 mg (66%) of the title compound as viscous oil: $[\alpha]_D^{21} +7.4^\circ$ (*c* 0.50, chloroform); EIMS (70eV) *m/z* (relative intensity) 405 (11, M⁺).

Example 84

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-ethylphenyl)benzamide

4'-Ethyl-4-biphenylcarboxylic acid (1.0 g, 4.4 mmol) was dissolved in thionyl chloride (15 mL) and heated at reflux for 1 h. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (130 mg, 0.53 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.48 mmol) and triethylamine (99 μ L, 0.72 mmol) in methylene chloride (20 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:4) as the eluent. Yield: 140 mg (53%) of the title compound as white crystals: mp 234-235 $^\circ$ C; $[\alpha]_D^{21} -73^\circ$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 453 (10, M⁺).

Example 85

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-hydroxyphenyl)benzamide

4'-Hydroxy-4-biphenylcarboxylic acid (0.40 g, 1.9 mmol) was dissolved in thionyl chloride (10 mL) and heated at reflux for 1 h. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (120 mg, 0.51 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-

1,2,3,4-tetrahydronaphthalene (120 mg, 0.49 mmol) and triethylamine (100 μ L, 0.74 mmol) in methylene chloride (20 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:6:0.5) as the eluent. Yield: 95 mg (44%) of the title compound as white crystals: mp 261-262 $^{\circ}\text{C}$; EIMS (70eV) m/z (relative intensity) 441 (2, M^+).

10 **Example 86**

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-trifluoromethylbenzamide

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.42 mmol) and triethylamine (88 μ L, 0.63 mmol) in methylene chloride (15 mL) was added dropwise 3-(trifluoromethyl)benzoyl chloride (93 mg, 0.44 mmol) in methylene chloride (5 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:4) as the eluent. Yield: 130 mg (71%) of the title compound as a viscous oil: $[\alpha]_D^{25} -25^{\circ}$ (c 1.0, chloroform); EIMS (70eV) m/z (relative intensity) 417 (25, M^+).

Example 87

25 **(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-phenoxybenzamide**

3-Phenoxybenzoic acid (1.0 g, 4.7 mmol) was dissolved in thionyl chloride (15 mL) and heated at reflux for 1 h. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (99 mg, 0.42 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an

ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (99 mg, 0.41 mmol) and triethylamine (83 μ L, 0.42 mmol) in methylene chloride (20 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. Yield: 120 mg (68%) of the title compound as an oil. The oil crystallized from diethyl ether/hexane: mp 136-137 $^\circ\text{C}$; $[\alpha]^{21}_{\text{D}} -9.0^\circ$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 441 (31, M^+).

Example 88

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-hydroxybenzamide

A solution of 3-acetoxybenzoic acid (130 g, 0.69 mol) in thionyl chloride (400 mL) was stirred at ambient temperature for 4 days. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (100 mg, 0.52 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.50 mmol) and triethylamine (100 μ L, 0.75 mmol) in methylene chloride (20 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was dissolved in 99.5% ethanol (25 mL) and concentrated hydrochloric acid (5 mL) was added. After 17 h, the pH was adjusted to 8 and the solvent evaporated *in vacuo*. The residue was partitioned between water and methylene chloride. The organic phase was separated, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:4) as the eluent. Yield: 93 mg (51%) of the title compound as white crystals: mp 117 $^\circ\text{C}$ decomp; $[\alpha]^{21}_{\text{D}} -10^\circ$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 365 (22, M^+).

Example 89**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-methylsulfonyloxybenzamide**

5 A suspension of 3-methanesulfonyloxybenzoic acid (0.20 g, 0.90 mmol; described in: Looker, J. H.; Hayes, C. H.; Thatcher, D. N. *J. Am. Chem. Soc.* **1957**, *79*, 741-4) in thionyl chloride (5 mL) was heated at 40 °C for 45 min (the solution became homogeneous). The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (120 mg, 0.50 mmol) was
10 dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.48 mmol) and triethylamine (100 µL, 0.72 mmol) in methylene chloride (20 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the
15 organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:4) as the eluent. Yield: 87 mg (41%) of the title compound as white crystals: mp 159-160 °C; [α]_D²¹ -27° (c 1.0, chloroform); EIMS⁺ (70eV) *m/z* (relative intensity) 443 (21, M⁺).

Example 90**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-2-methylbenzamide**

To an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.41 mmol) and triethylamine (85 µL, 0.62 mmol) in
25 methylene chloride (15 mL) was added dropwise 2-methylbenzoyl chloride (66 mg, 0.43 mmol) in methylene chloride (5 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol
30 saturated with NH₃ (100:3.5) as the eluent. Yield: 100 mg (80%) of the title compound as

white crystals: mp 179-180 °C; $[\alpha]^{21}_{\text{D}} -22^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 363 (21, M^+).

Example 91

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-2-ethoxybenzamide

To an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (110 mg, 0.43 mmol) and triethylamine (90 μL , 0.65 mmol) in methylene chloride (15 mL) was added dropwise 2-ethoxybenzoyl chloride (84 mg, 0.45 mmol) in methylene chloride (5 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with water. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:3) as the eluent. Yield: 110 mg (64%) of the title compound as white solid: $[\alpha]^{21}_{\text{D}} -36^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 393 (15, M^+). The hydrochloride salt was precipitated out of diethyl ether and 110 mg (59% yield) of white crystals were isolated; mp sinters at 176°C.

Example 92

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-2-hydroxybenzamide

To an ice-cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (180 mg, 0.74 mmol) and triethylamine (150 μL , 1.1 mmol) in methylene chloride (20 mL) was added dropwise acetylsalicyloyl chloride (160 mg, 0.78 mmol) in methylene chloride (10 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was dissolved in 99.5% ethanol (25 mL) and concentrated hydrochloric acid (3 mL) was added. After 17 h, the pH was adjusted to 8 and the solvent was evaporated *in vacuo*. The residue was partitioned between water and methylene chloride. The organic phase was separated, dried (Na_2SO_4), filtered and

evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent. Yield: 170 mg (63%) of the title compound as white crystals: mp 87 °C decomp; $[\alpha]_D^{21} -18^\circ$ (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 365 (33, M⁺).

Example 93

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-2-methylsulfonyloxybenzamide

A solution of 2-methanesulfonyloxybenzoic acid (0.30 g, 1.4 mmol; described in: Looker, J. H.; Hayes, C. H.; Thatcher, D. N. *J. Am. Chem. Soc.* **1957**, 79, 741-4) in thionyl chloride (10 mL) was heated at 40 °C for 45 min. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (120 mg, 0.49 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.47 mmol) and triethylamine (98 µL, 0.72 mmol) in methylene chloride (20 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the combined organic phases were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent. Yield: 110 mg (55%) of the title compound as white crystals: mp 144-145 °C; $[\alpha]_D^{21} -7.1^\circ$ (c 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 443 (10, M⁺).

Example 94

(R)-2-Amino-8-bromo-5-methoxy-1,2,3,4-tetrahydronaphthalene

(R)-2-Amino-5-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride (5.0 g, 23 mmol) was dissolved in acetic acid (300 mL) under nitrogen atmosphere. Sodium acetate (5.5 g, 70 mmol) was added and bromine (3.5 g, 23 mmol) was then added in one portion. The mixture was stirred for 5 minutes at room temperature. The solvent was removed *in vacuo* to give a solid residue which was partitioned between ethyl acetate and NaOH (2 M). The

layers were separated and the aqueous phase was extracted twice with ethyl acetate. The organic layers were combined and dried (Na₂SO₄). The solvent was removed *in vacuo* to give a brown oily residue. The HCl salt was precipitated from diethyl ether/methylene chloride by the addition of HCl in diethyl ether (3.M): yield 7.7 g (94%). Recrystallization
5 from methanol gave the title compound as needle crystals: mp 264-265 °C; [α]_D²¹ +54° (c 1, MeOH); EIMS (70eV) *m/z* (relative intensity) 257 (30, M⁺, ⁸¹Br), 255 (31, M⁺, ⁷⁹Br).

Example 95

(R)-8-Bromo-2-*N,N*-dibenzylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene

10 (R)-2-Amino-8-bromo-5-methoxy-1,2,3,4-tetrahydronaphthalene (4.5 g, 17.5 mmol), benzyl bromide (6.6 g, 38 mmol), potassium carbonate (9.7 g, 70 mmol) and potassium iodide (100 mg, catalytic amount) were mixed with acetonitrile (250 mL) under nitrogen atmosphere and refluxed for 18 h. The solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and ammonia (2 M). The layers were separated and the
15 organic layer was dried (MgSO₄). The solvent was removed *in vacuo* to give a residue which was purified by flash chromatography on silica gel using hexane/methylene chloride 8:2 as the eluent. The title compound was obtained as an oil. Yield 7.5 g (98%): [α]_D²¹ +87° (c 1, MeOH); EIMS (70eV) *m/z* (relative intensity) 437 (12, M⁺, ⁸¹Br), 435 (13, M⁺, ⁷⁹Br).

20

Example 96

(R)-2-*N,N*-Dibenzylamino-8-(1-methylpiperidin-4-yl)-5-trifluoromethanesulfonyloxy-1,2,3,4-tetrahydronaphthalene

(R)-8-Bromo-2-*N,N*-dibenzylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene (6.8 g, 16
25 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL) under nitrogen atmosphere. The solution was cooled to -78 °C before *n*-butyllithium (11.7 mL, 1.6 M, 19 mmol) was added dropwise during 3 minutes. The mixture was stirred for 5 minutes and *N*-methyl-4-piperidone (5.4 g, 48 mmol) was added during 3 minutes. The cooling bath was removed and the temperature was allowed to rise to 0 °C before the reaction was quenched by the
30 addition of water. The layers were separated and the organic layer was dried (MgSO₄). The

solvent was removed *in vacuo* to give a residue which was purified by crystallization (ethyl acetate/hexane) EIMS (70eV) *m/z* (relative intensity) 470 (2, M^+). The crystals were dissolved in tetrahydrofuran under nitrogen atmosphere. Sodium borohydride (5.9 g, 0.16 mol) was added and the mixture was cooled to 0 °C. Trifluoroacetic acid (10 mL) was added dropwise during 1h. The cooling bath was removed and the mixture was stirred for 1h at room temperature before it was carefully poured into a NaOH solution (40%-ig) and diluted with water and diethyl ether. The layers were separated and the organic layer was dried (MgSO₄). The solvent was removed *in vacuo* to give a solid residue [EIMS (70eV) *m/z* (relative intensity) 454 (12, M^+)] which was suspended in hydrobromic acid (48%, 200 mL) and refluxed (everything dissolved) for 2h. The mixture was allowed to attain room temperature. The formed crystals were filtered and partitioned between ethyl acetate and ammonia (2 M). The layers were separated and the organic layer was dried (MgSO₄). The solvent was removed *in vacuo* to give a solid residue [EIMS (70eV) *m/z* (relative intensity) 440 (5, M^+)] which was suspended in methylene chloride (150 mL). 2,4,6-Collidine (2 g, 16 mmol) was added and the mixture was cooled to -78 °C. Trifluoromethanesulfonic anhydride (4.4 g, 15 mmol) was added during 5 minutes. The cooling bath was removed and the temperature of the reaction mixture was allowed to rise to -5 °C. The reaction mixture was washed with ammonia (2 M) and dried (MgSO₄). The solvent was removed *in vacuo* to give a solid residue which was purified by flash chromatography on silica gel using methylene chloride/ethanol 10:1, containing 0.5% of ammonia, as the eluent. The title compound was obtained as an oil. Yield 4 g (44%): $[\alpha]^{21}_D +45^\circ$ (c 1, CHCl₃); EIMS (70eV) *m/z* (relative intensity) 572 (2, M^+).

Example 97

(*R*)-2-*N,N*-Dibenzylamino-8-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydronaphthalene
(*R*)-2-*N,N*-Dibenzylamino-8-(1-methylpiperidin-4-yl)-5-trifluoromethanesulfonyloxy-1,2,3,4-tetrahydronaphthalene (4 g, 7.0 mmol), triethylamine (2.8 g, 28 mmol), formic acid (1.3 g, 28 mmol), triphenylphosphine (0.4 g, 1.4 mmol) and palladium(II)acetate (85 mg, 0.35 mmol) were dissolved in *N,N*-dimethylformamide (20 mL) under nitrogen atmosphere. The solution was stirred at 60 °C for 18 h. The solvent was removed *in vacuo* to give a

residue which was partitioned between ethyl acetate and ammonia (2 M). The layers were separated and the organic layer was dried (MgSO₄). The solvent was removed *in vacuo* to give a dark brown oily residue which was purified by flash chromatography on silica gel using chloroform/ethanol 20:1, containing 0.5% of ammonia, as the eluent. The title
5 compound was obtained as an oil. Yield 1.7 g (57%): $[\alpha]^{21}_{\text{D}} +53^{\circ}$ (c 1, CHCl₃); EIMS (70eV) *m/z* (relative intensity) 424 (1, M⁺).

Example 98

(R)-2-Amino-8-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydronaphthalene

10 (R)-2-*N,N*-Dibenzylamino-8-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydronaphthalene (1.7 g, 4.0 mmol), ammonium formate (5.0 g, 80 mmol), palladium (10% on activated carbon, 0.8 g), methanol (30 mL), water (15 mL) and tetrahydrofuran (40 mL) were mixed under nitrogen atmosphere and refluxed for 3 h (fitted with an outlet for the excess of hydrogen gas). The catalyst was filtered off and washed thoroughly with ethanol. The solvent was
15 removed *in vacuo* until ca 30 mL was left. The residue was partitioned between ethyl acetate and NaOH (2 M). The layers were separated and the aqueous phase was extracted twice with ethyl acetate. The organic layers were combined and the solvent was removed *in vacuo* to give 0.8 g of the title compound as an oil (82% yield): $[\alpha]^{21}_{\text{D}} +36^{\circ}$ (c 0.5, CHCl₃); EIMS (70eV) *m/z* (relative intensity) 244 (1, M⁺).

20

Example 99

(R)-*N*-[8-(1-Methylpiperidine-4-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylbenzamide

α,α,α -Trifluoro-*p*-toluic acid (0.15 g, 0.8 mmol) was suspended in thionyl chloride (3 mL)
25 and refluxed for 30 minutes (everything dissolved after a few minutes). The excess of thionyl chloride was removed *in vacuo* with toluene. The residue was dissolved in methylene chloride (5 mL) and added dropwise to an ice cold solution of (R)-2-amino-8-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydronaphthalene (0.15 g, 0.6 mmol) and triethylamine (92 mg, 0.9 mmol) in methylene chloride (5 mL). The mixture was stirred for 15 minutes
30 and was then diluted with ethyl acetate, washed with ammonia (2 M) and dried (MgSO₄).

The solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel using methylene chloride/ethanol 5:1, containing 0.5% of ammonia, as the eluent. The title compound was obtained as off-white crystals. Yield 140 mg (55%); mp 163-166 °C; $[\alpha]^{21}_{\text{D}} +36^{\circ}$ (c 0.5, CHCl_3); EIMS (70eV) m/z (relative intensity) 416 (48, M^+).

5

Example 100

(R)-N-[8-(1-Methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-butoxybenzamide

4-Butoxybenzoic acid (0.16 g, 0.8 mmol) was dissolved in thionyl chloride (3 mL) and
10 refluxed for 30 minutes. The excess of thionyl chloride was removed *in vacuo* with toluene. The residue was dissolved in methylene chloride (5 mL) and added dropwise to an ice cold solution of (R)-2-amino-8-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydronaphthalene (0.15 g, 0.6 mmol) and triethylamine (92 mg, 0.9 mmol) in methylene chloride (5 mL). The mixture was stirred for 30 minutes and was then diluted with ethyl acetate, washed with ammonia (2
15 M) and dried (MgSO_4). The solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel using methylene chloride/ethanol 5:1, containing 0.5% of ammonia, as the eluent. The title compound was obtained as white crystals. Yield 170 mg (50%); mp 162-164 °C; $[\alpha]^{21}_{\text{D}} -2^{\circ}$ (c 0.5, CHCl_3); EIMS (70eV) m/z (relative intensity) 420 (40, M^+).

20

Example 101

(R)-N-[8-(1-Methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide

4-N-Morpholinobenzoic acid (0.4 g, 1.6 mmol) was dissolved in thionyl chloride (5 mL)
25 under nitrogen atmosphere and stirred at room temperature for 5 minutes. The excess of thionyl chloride was removed *in vacuo* to give a light yellow residue. The residue was dissolved in methylene chloride (10 ml) and added dropwise to a solution of (R)-2-amino-8-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydronaphthalene (0.4 g, 1.9 mmol) and triethylamine (0.4 g, 4.0 mmol) in methylene chloride (10 mL) during 5 minutes. The mixture was stirred
30 at room temperature for 15 minutes before washed with 2 M ammonia and dried (MgSO_4).

The solvent was removed *in vacuo* to give a residue which was purified by flash chromatography on silica gel using methylene chloride/ethanol, 5:1 containing 0.5% of ammonia. Yield 100 mg (12%): mp 196-198 °C; $[\alpha]^{21}_{\text{D}} -19^{\circ}$ (*c* 1, CHCl₃); EIMS (70eV) *m/z* (relative intensity) 433 (27, M⁺).

5

Example 102

(R)-2-N,N-Dibenzylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene

To a solution of (R)-5-methoxy-2-amino-1,2,3,4-tetrahydronaphthalene hydrochloride (30 g, 0.14 mol) in acetonitrile (600 mL) were added potassium carbonate (68 g, 0.49 mol),
10 potassium iodide (catalytic amount) and benzyl bromide (42 mL, 0.35 mol). The reaction mixture was stirred at reflux for a period of 48 h.

After the precipitate was filtered off and the acetonitrile removed *in vacuo*, the residue was partitioned between diethyl ether and water. The organic phase was separated, dried (Na₂SO₄) and evaporated *in vacuo* to give a crude product which was purified on a silica
15 gel column using hexane/ethyl acetate, (3:1) as the eluent. Yield: 46 g (92%) of the title compound as white crystals: mp 112-114 °C; $[\alpha]^{21}_{\text{D}} +61^{\circ}$ (*c* 1.0, chloroform); EIMS (70 eV) *m/z* (relative intensity) 357 (38, M⁺).

Example 103

(S)-2-N,N-Dibenzylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene

The title compound was synthesized according to the procedure of Example 102 using the (S)-form: mp 113-115 °C; $[\alpha]^{21}_{\text{D}} -59^{\circ}$ (*c* 1.0, chloroform); EIMS (70 eV) *m/z* (relative intensity) 357 (74, M⁺).

Example 104

(R)-6-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthol

(R)-2-N,N-Dibenzylamino-5-methoxy-1,2,3,4-tetrahydronaphthalene (46 g, 0.13 mol) was dissolved in diethyl ether (900 mL) and an excess of an ethereal HCl solution was added dropwise. The precipitate was filtered and dried *in vacuo* to give a white solid. This crude
30 product (45 g, 0.11 mol)

was dissolved in anhydrous methylene chloride (500 mL) and cooled to -60 °C. To the solution was boron tribromide (14 mL, 0.15 mol), dissolved in anhydrous methylene chloride (50 mL), added dropwise. The reaction temperature was allowed to reach -5 °C and was kept there overnight.

- 5 To the ice-cooled solution was a 2 M aqueous ammonium hydroxide solution added dropwise and the mixture was extracted, twice, with methylene chloride. The combined organic phases were dried (Na₂SO₄), filtered and the solvent was removed *in vacuo* to give the crude residue. Chromatography on silica (eluent: methylene chloride) gave 33 g (83% yield) of the title compound as a viscous clear oil: $[\alpha]^{21}_{\text{D}} +72^{\circ}$ (c 0.66, chloroform); EIMS
10 (70eV) *m/z* (relative intensity) 343 (11, M⁺).

Example 105

(S)-6-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthol

- The title compound was synthesized according to the procedure of Example 104 using the
15 (S)-form: $[\alpha]^{21}_{\text{D}} -71^{\circ}$ (c 0.71, chloroform); EIMS (70eV) *m/z* (relative intensity) 343 (12, M⁺).

Example 106

- (R)-2-(6-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyloxy)-2-methylpropanamide**
20

- (R)-6-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthol (28 g, 81 mmol) was stirred in anhydrous dioxane (500 mL) with sodium hydride (60-65% in oil, 2.2 g, 90 mmol) for 1 h. 2-Bromo-2-methylpropanamide (15 g, 90 mmol; described in: Coutts, I. G. C.; Southcott, M.R. *J. Chem. Soc. Perkin Trans. 1* **1990**, 767-770) was added and the reaction mixture
25 was heated at 80 °C for 2.5 h. After cooling, the precipitated sodium bromide was filtered off, the filtrate evaporated *in vacuo* and the residue was partitioned between water and methylene chloride. The organic phase was separated, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a viscous oil. Yield: 24 g (70% yield). This crude product was used directly in the next step without further purification. An
30 analytical sample (0.50 g) was purified on a silica gel column using hexane/ethyl acetate

(3:1) as the eluent. Yield: 0.46 g of the title compound as a viscous oil: $[\alpha]^{21}_{\text{D}} +42^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 428 (1, M^+).

Example 107

5 **(*S*)-2-(6-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyloxy)-2-methylpropanamide**

The title compound was synthesized according to the procedure of Example 106 using the (*S*)-form: $[\alpha]^{21}_{\text{D}} -42^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 428 (8, M^+).

10

Example 108

(*R*)-*N*-(6-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-2-hydroxy-2-methylpropanamide

To a solution of (*R*)-2-(6-*N,N*-dibenzylamino-5,6,7,8-tetrahydro-1-naphthyloxy)-2-methylpropanamide (23 g, 54 mmol) in anhydrous 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (10 mL) and dry *N,N*-dimethylformamide (250 mL) was added sodium hydride (60-65% in oil, 5.4 g, 135 mmol) and the reaction was heated at 130 °C for 10 h. An additional amount of anhydrous 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (15 mL) and sodium hydride (0.5 mol equiv.) was added and the reaction was heated at 130 °C for in total 21 h. The solution was poured into a mixture of ice and water and extracted three times with ethyl acetate. The combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a viscous oil. Yield: 20 g (86% yield). This crude product was used directly in the next step without further purification. An analytical sample (0.50 g) was purified on a silica gel column using hexane/ethyl acetate (5:1) as the eluent. Yield: 0.24 g of the title compound as a viscous oil: $[\alpha]^{21}_{\text{D}} +35^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 428 (1, M^+).

15
20
25

Example 109

(S)-N-(6-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-2-hydroxy-2-methylpropanamide

The title compound was synthesized according to the procedure of Example 108 using the
5 (S)-form: $[\alpha]^{21}_D +33^\circ$ (c 1.1, chloroform); EIMS (70eV) m/z (relative intensity) 428 (4, M^+).

Example 110

(R)-2-N,N-Dibenzylamino-5-amino-1,2,3,4-tetrahydronaphthalene

10 (R)-N-(6-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-2-hydroxy-2-methylpropanamide (19 g, 44 mmol) was dissolved in ethanol (500 mL) and a 20% HCl aqueous solution (500 mL) and heated to reflux for 18 h. The ethanol was evaporated *in vacuo* and the remaining solution was washed twice with diethyl ether and cooled on ice-bath. After alkalization with a 45% aqueous solution of sodium hydroxide the mixture was
15 extracted with methylene chloride. The combined organic phases were dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification on a silica gel column using chloroform as the eluent gave 6.1 g (40% yield) of the title compound as a light-brown viscous oil: $[\alpha]^{21}_D +54^\circ$ (c 0.97, chloroform); EIMS (70eV) m/z (relative intensity) 342 (19, M^+).

20 **Example 111**

(S)-2-N,N-Dibenzylamino-5-amino-1,2,3,4-tetrahydronaphthalene

The title compound was synthesized according to the procedure of Example 110 using the
(S)-form: $[\alpha]^{21}_D -53^\circ$ (c 1.0, chloroform); EIMS (70eV) m/z (relative intensity) 342 (20, M^+).

25

Example 112

(R)-1-(6-N,N-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-4-methylpiperazine-2,6-dione

1,1'-Carbonyldiimidazole (5.5 g, 34 mmol) was added to a stirred suspension of
30 methyliminodiacetic acid (2.5 g, 17 mmol) in anhydrous *N,N*-dimethylformamide (250 mL).

The reaction mixture was heated at 80 °C for 1 h. (R)-2-*N,N*-Dibenzylamino-5-amino-1,2,3,4-tetrahydronaphthalene (5.3 g, 15 mmol) dissolved in anhydrous *N,N*-dimethylformamide (75 mL) was then added and stirring at 80 °C was continued for 10 h. The solvent was evaporated *in vacuo* and the crude product was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:0.5) as the eluent. Yield: 5.0 g (87% yield) as a viscous oil: $[\alpha]^{21}_{\text{D}} +51^{\circ}$ (*c* 1.1, chloroform); EIMS (70eV) *m/z* (relative intensity) 453 (16, M⁺).

Example 113

10 (S)-1-(6-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-4-methylpiperazine-2,6-dione

The title compound was synthesized according to the procedure of Example 112 using the (S)-form: $[\alpha]^{21}_{\text{D}} -50^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 453 (22, M⁺).

15

Example 114

(R)-2-*N,N*-Dibenzylamino-5-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (R)-1-(6-*N,N*-Dibenzylamino-5,6,7,8-tetrahydro-1-naphthyl)-4-methylpiperazine-2,6-dione (4.0 g, 8.8 mmol) was added to a suspension of lithium aluminium hydride (1.7 g, 44 mmol) in anhydrous tetrahydrofuran (125 mL). The reaction mixture was heated at reflux for 5 h. The reaction was quenched by the addition of water (1.7 mL), 15% aqueous sodium hydroxide (1.7 mL) and again water (5.1 mL). The mixture was filtered, dried (Na₂SO₄) and evaporated *in vacuo*. Purification on a silica gel column using chloroform/ethanol saturated with NH₃ (100:1) as the eluent gave 1.4 g (38% yield) of the title compound as a viscous oil: $[\alpha]^{21}_{\text{D}} +7.0^{\circ}$ (*c* 1.0, chloroform); EIMS (70 eV) *m/z* (relative intensity) 425 (7, M⁺).

25

Example 115**(S)-2-N,N-Dibenzylamino-5-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

The title compound was synthesized according to the procedure of Example 114 using the (S)-form: $[\alpha]^{21}_D -8.0^\circ$ (c 1.1, chloroform); EIMS (70 eV) m/z (relative intensity) 425 (6, M^+).

Example 116**(R)-2-Amino-5-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

To a solution of (R)-2-N,N-dibenzylamino-5-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (1.3 g, 3.0 mmol) in methanol (70 mL) were added ammonium formate (4.6 g, 73 mmol) and palladium (10%) on activated carbon (0.45 g). The mixture was refluxed for 2 h and the palladium was then filtered off. The solvent was evaporated *in vacuo* and the residue was purified on a silica gel column using chloroform/methanol/concentrated ammonium hydroxide (95:5:05) as the eluent. Yield: 360 mg (49%) as lightbrown crystals: mp 98-99 °C; $[\alpha]^{21}_D +21^\circ$ (c 1.1, chloroform); EIMS (70 eV) m/z (relative intensity) 245 (41, M^+).

Example 117**(S)-2-Amino-5-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene**

The title compound was synthesized according to the procedure of Example 116 using the (S)-form: mp 97-98 °C; $[\alpha]^{21}_D -21^\circ$ (c 1.1, chloroform); EIMS (70 eV) m/z (relative intensity) 245 (55, M^+).

Example 118**(R)-N-[5-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide**

To a solution of 4-morpholinobenzoic acid (110 mg, 0.51 mmol) in anhydrous *N,N*-dimethylformamide (10 mL) was added 1,1'-carbonyldiimidazole (87 mg, 0.54 mmol) and the reaction was heated at 75 °C. When the carbon dioxide evolution had ceased (after 30 min), the reaction was cooled to room temperature and a solution of (R)-2-amino-5-(4-

methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.49 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added. The reaction was allowed to stir at 70 °C for 18 h and the solvent was evaporated *in vacuo*. The residue was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent. This gave after
5 crystallization from acetonitrile, 65 mg (30% yield) of the title compound as white crystals: mp 127-128 °C; [α]²¹_D +51° (*c* 0.50, chloroform); EIMS (70 eV) *m/z* (relative intensity) 434 (14, M⁺).

Example 119

10 **(*S*)-*N*-[5-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide**

The title compound was synthesized according to the procedure of Example 118 using the (*S*)-form: mp 129-131 °C; [α]²¹_D -52° (*c* 0.50, chloroform); EIMS (70 eV) *m/z* (relative intensity) 434 (8, M⁺).

15

Example 120

(*R*)-*N*-[5-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-phenoxybenzamide

3-Phenoxybenzoic acid (1.0 g, 4.7 mmol) was dissolved in thionyl chloride (15 mL) and
20 heated at reflux for 30 min. The excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (70 mg, 0.30 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (*R*)-2-amino-5-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (70 mg, 0.28 mmol) and triethylamine (55 μ L, 0.42 mmol) in
25 methylene chloride (25 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH₃ (100:3) as the eluent. Yield: 45 mg (36%) of

the title compound as a solid foam: $[\alpha]^{21}_{\text{D}} +24^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 441 (18, M^+).

Example 121

5 **(S)-N-[5-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-phenoxybenzamide**

The title compound was synthesized according to the procedure of Example 120 using the (S)-form: $[\alpha]^{21}_{\text{D}} -23^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 441 (20, M^+).

10 Example 122

(R)-N-Methyl-N-[8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylbenzamide

To an ice-cooled solution (R)-2-N-methylamino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (100 mg, 0.39 mmol) and triethylamine (80 μL , 0.58 mmol) in
15 methylene chloride (25 mL) was 4-(trifluoromethyl)benzoyl chloride (90 mg, 0.43 mmol) in methylene chloride (5 mL) added dropwise. After the addition the reaction was allowed to stir at ambient temperature for 15 min and was then washed with diluted aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4),
20 filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (100:2) as the eluent. Yield: 89 mg (53%) of the title compound as a colourless crystals: mp 123-125 $^{\circ}\text{C}$; $[\alpha]^{21}_{\text{D}} +104^{\circ}$ (*c* 1.0, chloroform); EIMS (70eV) *m/z* (relative intensity) 431 (13, M^+).

25 Example 123

(R)-8-(4-Methylpiperazin-1-yl)-2-[N-(4-trifluoromethyl)benzylamino]-1,2,3,4-tetrahydronaphthalene

To a solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (200 mg, 0.81 mmol) in acetonitrile (35 mL) were added potassium carbonate (169 mg, 1.2

mmol), potassium iodide (catalytic amount) and 4-(trifluoromethyl)benzyl bromide (194 mg, 0.81 mmol). The reaction mixture was stirred at reflux for a period of 8 h.

After the precipitate was filtered off and the acetonitrile removed *in vacuo*, the residue was purified on a silica gel column using chloroform/methanol

5 /concentrated ammonium hydroxide (95:5:0.5) as the eluent. Yield: 72 mg (22%) of the title compound as a colourless oil: $[\alpha]^{21}_{\text{D}} +12^{\circ}$ (c 1.0, chloroform); EIMS (70 eV) *m/z* (relative intensity) 403 (1, M^{+}).⁺ The oxalate salt was precipitated out of diethyl ether and light brown crystals were isolated. Yield: 81 mg (17%): mp 95 °C, sinters.

10

Example 124

4-Thiomorpholinobenzoic Acid

To a solution of 4-thiomorpholinobenzonitrile (1 g, 4.9 mmol; described in: Beach, S. F.; Hepworth, J. D.; Sawyer, J.; Hallas, G.; Marsden, R.; Mitchell, M. M.; Ibbitson, D. A.;
15 Jones, A. M.; Neal, G. T. *J. Chem. Soc. Perkin Trans. II*, **1984**, 217-221) in glacial acetic acid (20 mL) was added a 20% aqueous hydrochloric acid solution (20 mL) and the reaction was heated at reflux for 15 h. The acetic acid was evaporated *in vacuo* and the remaining water solution was alkalized with 2 M aqueous sodium hydroxide solution to pH 12. The solution was washed, twice, with diethyl ether and the water phase was adjusted to
20 pH 3 with a 20% aqueous hydrochloric acid solution. The product was filtered off and dried *in vacuo* to afford 1.0 g (91% yield) of the title compound as white crystals: mp 233-235 °C; EIMS (70eV) *m/z* (relative intensity) 223 (50, M^{+}).

Example 125

25 **(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-thiomorpholinobenzamide**

4-Thiomorpholinobenzoic acid (0.25 g, 1.1 mmol) was dissolved in thionyl chloride (25 mL). The excess of thionyl chloride was immediately evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. Crude acid chloride (107
30 mg, 0.44 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to an ice-

cooled solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (104 mg, 0.42 mmol) and triethylamine (68 μ L, 0.87 mmol) in methylene chloride (35 mL). After the addition the reaction was allowed to stir at ambient temperature for 15 min and then washed with diluted aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using chloroform/methanol/ concentrated ammonium hydroxide (95:5:0.5) as the eluent. Yield: 58 mg (31%) of the title compound as white crystals: mp 190-191 °C; $[\alpha]^{21}_{\text{D}} -86^\circ$ (c 0.25, chloroform); EIMS (70eV) *m/z* (relative intensity) 450 (2, M^+).

Example 126

4-(4-Benzylpiperazin-1-yl)benzonitrile

To a solution of 4-fluorobenzonitrile (3.0 g, 25 mmol) in *N,N*-dimethylformamide (15 mL) were added 1-benzylpiperazine (4.3 mL, 25 mmol) and potassium carbonate (3.4 g, 25 mmol). The reaction mixture was stirred at 120°C for 13 h. The solvent was evaporated and the residue was partitioned between ethyl acetate (100 mL) and water (15 mL). The aqueous phase was extracted with ethyl acetate (30 mL) and the combined organic phases were washed twice with brine (10 mL) and dried (MgSO_4). Evaporation of the solvent gave 7.6 g of crude product. Purification of the residue on a silica column using ethyl acetate/methylene chloride (1:9) as the eluent afforded 4.0 g (59% yield) of the title compound as a white solid: mp 104-105°C; EIMS (70eV) *m/z* (relative intensity) 277 (20, M^+).

Example 127

4-(4-Benzylpiperazin-1-yl)benzoic acid

4-(4-Benzylpiperazin-1-yl) benzonitrile (4.0 g, 15 mmol) was dissolved in glacial acetic acid (40 mL), 6 M hydrochloric acid (50 mL) was added and the reaction mixture was stirred at 100° C for 17 h. The solvent was evaporated, the residue was suspended in water (10 mL) and the pH was adjusted to 3 by addition of 2 M sodium hydroxide (35 ml). The slurry was stirred at 50° C for 2 h, cooled and the precipitate was filtered and dried *in vacuo* to give 4.1

g of a crude product. The solid was partitioned between methylene chloride (40 mL) and water (220 mL) with 2 M sodium hydroxide (8 mL). The aqueous phase was washed with methylene chloride (40 mL) and the pH was adjusted to 5 with 2 M hydrochloric acid. The aqueous phase was cooled, the precipitate was filtered and dried *in vacuo* to give 1.6 g (38% yield) of the title compound: mp 226° C (dec); EIMS (70 eV) m/z (relative intensity) 296 (44, M⁺).

Example 128

(R)-N-8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl-4-(4-benzylpiperazin-1-yl)benzamide

A suspension of 4-(4-benzylpiperazin-1-yl)benzoic acid (57 mg, 0.19 mmol) and 1,1'-carbonyldiimidazole (33 mg, 0.20 mmol) in *N,N*-dimethylformamide (2 mL) was stirred at 75° C for 2 h. The solution was cooled and (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (45 mg, 0.18 mmol), dissolved in *N,N*-dimethylformamide (1 mL), was added. The reaction mixture was stirred at ambient temperature for 40 h. The solvent was evaporated and the residue was dried *in vacuo* to give 149 mg of a crude product. Purification of the residue by preparative TLC (silica) eluting with chloroform/ethanol saturated with NH₃ (15:1) as the eluent gave 63 mg (63% yield) of the title compound as a white solid: mp 209-210° C; [α]_D²¹ -65° (c 0.5, chloroform); EIMS (70 eV) m/z (relative intensity) 523 (13, M⁺).

Example 129

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinocarbonylbenzamide

4-Morpholinocarbonylbenzoic acid (130 mg, 0.54 mmol; described in: *J. Med. Chem.* **1994**, 37(26), 4538-4554) was dissolved in thionyl chloride (5 mL). When the acid was dissolved, the excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. The crude acid chloride was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazine-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.49 mmol) and

triethylamine (100 μ L, 0.73 mmol) in methylene chloride (20 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using using chloroform/methanol/concentrated ammonium hydroxide (95:4:0.5) as the eluent. Yield: 160 mg (72%) of the title compound as white crystals: mp 124-127 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{21} -40^{\circ}$ (c 1.0, chloroform); EIMS (70eV) m/z (relative intensity) 462 (2, M^+).

10 **Example 130**

(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(N,N-dimethylaminocarbonyl)benzamide

4-(N,N-Dimethylaminocarbonyl)benzoic acid (100 mg, 0.54 mmol; described in: patent US 3607918, 1971) was dissolved in thionyl chloride (5 mL). When the acid was dissolved, the excess of thionyl chloride was evaporated *in vacuo*, the residue was treated with toluene and again the solvent was removed *in vacuo*. The crude acid chloride was dissolved in methylene chloride (5 mL) and added dropwise to an ice-cooled solution of (R)-2-amino-8-(4-methylpiperazine-1-yl)-1,2,3,4-tetrahydronaphthalene (120 mg, 0.49 mmol) and triethylamine (100 μ L, 0.73 mmol) in methylene chloride (20 mL). After the addition, the reaction was allowed to stir at ambient temperature for 15 min and was then washed with dilute aqueous sodium hydrogen carbonate. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give a crude product which was purified on a silica gel column using using chloroform/methanol/concentrated ammonium hydroxide (95:4:0.5) as the eluent. Yield: 160 mg (79%) of the title compound as white foam: $[\alpha]_{\text{D}}^{21} -30^{\circ}$ (c 1.0, chloroform); EIMS (70eV) m/z (relative intensity) 420 (10, M^+).

Example 131**4-(4-Piperidon-1-yl)benzoic acid**

A solution of 2 M NaOH (10 mL), 4-(8-aza-1,4-dioxaspiro[4,5]dec-8-yl)benzonitrile (820 mg, 3.4 mmol; described in: Taylor E. C.; Skotnicki J. S. *Synthesis* **1981**, 8, 606-608), and ethanol (7.5 mL) was heated at reflux for 3 h. The external heating was interrupted and the reaction mixture was stirred overnight at ambient temperature. The ethanolic solvent was removed *in vacuo* and the remains were acidified to pH 4 with 2 M HCl followed by extraction with ethyl acetate (50 mL). The layers were separated, and the pH was adjusted to 6 with 2 M NaOH followed by another extraction with ethyl acetate (50 mL). The combined organic layers were concentrated *in vacuo*, and the solid residue was dissolved in 6 M HCl (10 mL). The reaction mixture was stirred at 75 °C for 2.5 h and at 55 °C overnight. The temperature was raised to 75 °C for 2 h, and the reaction mixture was then allowed to cool. The pH was adjusted to 4 and the solution was extracted with ethyl acetate (50 mL). The layers were separated and pH was adjusted to 5 followed by another extraction with ethyl acetate. The combined organic layers were dried (MgSO₄) and the solvent was removed *in vacuo*. The crude product was recrystallized from ethyl acetate affording 300 mg (41% yield) of the title compound as yellowish crystals: mp >215 °C (sinters); EIMS (70 eV) *m/z* (relative intensity) 219 (M⁺, 100)

Example 132**(R)-N-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-piperidon-1-yl)benzamide**

4-(Piperidon-1-yl)benzoic acid (230 mg, 1.0 mmol) and *N,N*-diisopropylethylamine (180 µL, 1.0 mmol) were dissolved in dry *N,N*-dimethylformamide (10 mL) and cooled to -20 °C. Isobutylchloroformate (130 µL, 1.0 mmol) was added and the reaction mixture was stirred for 1 h. A solution of (R)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene in *N,N*-dimethylformamide (2 mL) was added and the reaction mixture was stirred at -20 °C for 30 min and at room temperature for 1 h. The solvent was evaporated and the residue was partitioned between ethyl acetate (100 mL) and 2 M NH₃ (15 mL). The organic phase was washed with brine (15 mL), dried (MgSO₄) and the

solvent was evaporated to give 390 mg of a crude product. Purification by column chromatography on silica using chloroform/methanol/conc. NH_3 (950:50:5) and chloroform/ethanol saturated with NH_3 (15:1) as eluents afforded 124 mg (27% yield) of the title compound as a white solid: mp $>223^\circ\text{C}$ (sinters); EIMS (70 eV) m/z (relative intensity) 446 (M^+ , 8); $[\alpha]^{22}_{\text{D}} -78^\circ$ (c 0.28, chloroform).

Example 133

3',4'-Dihydro-8'-[4-methyl(piperazin-1-yl)]-spiro-[1,3-dioxolane-2,2'(1H)-naphthalene].

8'-Bromo-3',4'-dihydrospiro-[1,3-dioxolane-2,2'(1H)-naphthalene] (6.0 g, 22 mmol; described in Sunkyung L.; Stewart P.F.; David E.N. *Synth. Commun.* **1995**, 25(18), 2775-2780) was dissolved in toluene (180 mL) and flushed with argon. *N*-Methylpiperazine (3.0 mL, 27 mmol), R(+)-bis(diphenylphosphino)-1,1'-binaphthyl (830 mg, 1.3 mmol), tetrakis(dibenzylideneacetone)dipalladium (0) (510 mg, 0.45 mmol) and sodium *t*-butoxide (3.0 g, 31 mmol) were added and the reaction mixture was stirred at 85°C for 2.5 h. After cooling to room temperature ethyl acetate (400 mL) and 2 M ammonia (60 mL) were added. The phases were separated and the organic layer was washed with 2 M ammonia (30 mL), brine (40 mL) and dried (MgSO_4). Evaporation of the solvent gave 7.5 g of a crude product. Purification by column chromatography on silica using chloroform/ methanol/conc. NH_3 (180:5:0.5) as eluent afforded 5.5 g (84% yield) of the title compound as a yellowish solid: mp $127\text{--}128^\circ\text{C}$; EIMS (70 eV) m/z (relative intensity) 288 (43, M^+).

Example 134

8-[4-Methyl(piperazin-1-yl)]-2-tetralone.

3',4'-Dihydro-8'-[4-methyl(piperazin-1-yl)]-spiro-[1,3-dioxolane-2,2'(1H)-naphthalene] (1.0 g, 3.5 mmol) was dissolved in freshly distilled tetrahydrofuran (50 mL) and the solution was cooled to 0°C . To the solution was added 2 M hydrochloric acid (10 mL) and after 5 min the cooling bath was removed. The reaction mixture was stirred at ambient temperature for 3.5 h. Tetrahydrofuran was removed *in vacuo* and the residue was mixed with methylene chloride (100 mL) and cooled on ice-bath. To the mixture was added 2 M

sodium hydroxide (10 mL) and the phases were separated. The organic layer was washed with brine (15 mL) and dried (MgSO₄). The solvent was evaporated giving 810 mg (95% yield) of the title compound as a brownish crystalline solid: mp > 85 °C (sinters) ; EIMS (70 eV) *m/z* (relative intensity) 244 (51, M⁺).

5 **Example 135**

2-Cyano-3,4-dihydro-8-[4-methyl(piperazin-1-yl)]-naphthalene.

8-[4-Methyl(piperazin-1-yl)]-2-tetralone (420 mg, 1.7 mmol) was dissolved in diethyl ether (50 mL) and precipitated by the addition of 3 M HCl in diethyl ether (1 mL, 3 mmol). The solvent was evaporated giving 520 mg of the salt.

10 The precipitate was mixed with water (20 mL) and an aqueous solution of potassium cyanide (450 mg, 7.0 mmol in 15 mL) was added giving a slurry. The reaction mixture was stirred for 2.5 h, 2 M hydrochloric acid (400 µL, 0.8 mmol) was added. After an additional 30 min, the slurry (pH~10) was extracted with ethyl acetate (100 mL). The organic phase was washed with water (15 mL) and brine (15mL) and dried (MgSO₄). Evaporation of the
15 solvent gave 460 mg of the crude cyanohydrin. The crude material was dissolved in pyridine (10 mL) and cooled to 0 °C. Phosphorus oxychloride (320 µL, 3.5 mmol) was added and the reaction mixture was stirred at 0 °C for 20 min. The cooling bath was removed and the reaction mixture was stirred at room temperature for 13 h. The solvent was evaporated and the residue was mixed with water (15 mL) and pH was adjusted to 11 with 2 M sodium
20 hydroxide. Extraction with ethyl acetate (120 mL), washing the organic phase with water (15 mL) and brine (15 mL), drying (MgSO₄), followed by evaporation of the solvent gave 380 mg of a crude product. Purification by column chromatography on silica using chloroform/methanol/conc. NH₃ (180:5:0.5) as eluent gave 330 mg (75% yield) of the title compound as a yellowish solid: mp 104-105 °C; EIMS (70 eV) *m/z* (relative intensity) 253
25 (47, M⁺).

Example 136

2-Cyano-1,2,3,4-tetrahydro-8-[4-methyl(piperazin-1-yl)]naphthalene.

2-Cyano-3,4-dihydro-8-[4-methyl(piperazin-1-yl)]-naphthalene (230 mg, 0.90 mmol) was dissolved in dry methanol (15 mL) and cooled to 0 °C. Magnesium turnings (440 mg, 18
30 mmol) was added and the reaction mixture was stirred for 45 min at 0 °C and for 4 h, at

room temperature. The solvent was evaporated and 2 M hydrochloric acid (20 mL) was added to the residue. The mixture was stirred for 1 h, cooled on ice-bath and alkalized to pH 10 with 2 M ammonia. The solution was extracted with ethyl acetate (60 + 2x30 mL) and the organic phase was washed with brine (15 mL). Drying (MgSO₄) and evaporation of the solvent gave 210 mg of a crude product. Purification by preparative TLC on silica using chloroform/methanol/conc. NH₃ (95:5:0.5) afforded 160 mg (71% yield) of the title compound as a white solid: mp 111-112 °C; EIMS (70 eV) *m/z* (relative intensity) 255 (34, M⁺).

10 Example 137

***N*-(4-Morpholinocarbonylphenyl)-8-[4-(methylpiperazin-1-yl)]-1,2,3,4-tetrahydronaphthalene-2-carboxamide.**

2-Cyano-1,3,4-trihydro-8-[4-(methylpiperazin-1-yl)]naphthalene (170 mg, 0.67 mmol) was dissolved in methanol (2 mL) and 2 M sodium hydroxide (1.7 mL, 3.4 mmol) was added. The reaction mixture was heated at reflux for 1 h and then concentrated to about half the volume. The mixture was stirred at 100 °C for 8 h followed by cooling on ice. 2 M sodium hydroxide (1.7 mL, 3.4 mmol) was added giving a thick slurry. Water was removed by a stream of nitrogen and the solid was dried at 60 °C *in vacuo*. The crude product was stirred with *N,N*-dimethyl formamide (10 mL) at 90 °C for 10 min and insoluble material was filtered off. The solvent was evaporated and the residue was dried at 60 °C *in vacuo* to give 179 mg (97% yield) of the crude acid: CIMS (CH₄) *m/z* (relative intensity) 275 (100, M⁺⁺¹). The acid (119 mg, 0.43 mmol) was mixed with *N,N*-dimethyl formamide (2 mL). 4-methylmorpholine (95 µL, 0.86 mmol) was added and the mixture was cooled to 0 °C. Diphenylphosphinic chloride (91 µL, 0.43 mmol) was added and the reaction mixture was stirred for 5 min on ice-bath and for 7 h at room temperature. 4-(Morpholinocarbonyl)aniline (89 mg, 0.43 mmol; described in Delvin J.P. et al. *J. Chem. Soc. Perkin Trans. 1*. **1975** (9) 830-841) was added and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated and the residue was partitioned between ethyl acetate (60 mL) and 2 M ammonia (5 mL). The organic phase was washed with brine (5 mL) and dried (MgSO₄). The solvent was evaporated giving 185 mg of a

crude product. Purification by preparative TLC on silica using chloroform/methanol/ conc. NH₃ (180:5:0.5) as eluent afforded 70 mg (35% yield) of the title compound as a white foam: EIMS (70 eV) *m/z* (relative intensity) 462 (49, M⁺).

5 **Example 138**

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-morpholinomethyl)benzamide

4-(4-Morpholinomethyl)benzoic acid (91 mg, 0.41 mmol; described in Grabenko, A. D; Shevchenko, L. I; Pelkis, P. S. *Fiziol. Akt. Veshchestva* **1976**, 8, 78-83) and 1,1'-carbonyldiimidazole (70 mg, 0.43 mmol) were dissolved in dry *N,N*-dimethylformamide (3 mL) and stirred at 75 °C for 2 h. The reaction mixture was cooled to 50 °C and a solution of (*R*)-2-amino-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (96 mg, 0.39 mmol) in dry *N,N*-dimethylformamide (2 mL) was added. The reaction mixture was stirred at 50 °C for 60 h followed by evaporation of the solvent and drying *in vacuo* giving 290 mg of a crude product. Purification by column chromatography on silica using chloroform/methanol/conc. NH₃ (95:5:0.5) as the eluent followed by recrystallization from ethyl acetate (3 mL) and diethyl ether (2 mL) afforded 40 mg (23% yield) of the title compound as a white solid: mp 173-174 °C; EIMS (70 eV) *m/z* (relative intensity) 448 (18, M⁺); [α]_D²¹ -0.8° (c 0.20, chloroform).

20 **PHARMACOLOGY**

Potassium(K⁺) or electrical field stimulation of [³H] -5-HT release from occipital cortex of guinea pigs

[³H] -5-HT is released by electrical field stimulation from slices of occipital cortex of guinea pigs which have been pre-incubated with [³H] -5-HT. This release is similar to that caused by nerve stimulation, i.e. exocytotic release from serotonergic nerve terminals, depending on the presence of Ca²⁺ in the incubation medium. In the guinea pigs (like in humans) the 5-HT release is regulated at the level of the nerve terminals by autoreceptors, belonging to the 5-HT_{1D} receptor subtype. Thus, agonists of 5-HT_{1D} receptors reduce the amount of [3H]-

5-HT released by (K^+) or field stimulation whereas the release is increased by antagonists of this receptor type. Testing compounds with this method is accordingly a convenient screening technique for determining the potency and functional effect of new 5-HT_{1D} receptor agonists and antagonists.

Methods and Materials

Buffer composition (mM) NaHCO₃ (25), NaH₂PO₄·H₂O (1.2), NaCl (117), KCl(6), MgSO₄·7H₂O(1.2), CaCl₂(1.3), EDTA Na₂(0.03). The buffer is gassed for at least 30 min before use. The pH of the buffer is about 7.2 of room temperature but it rises to about 7.4 at 37°C.

Preparation of occipital cortical slices

Guinea pigs (200-250 g) were decapitated and the whole brains were removed. The occipital cortices were dissected and cut into slices 0.4x4 mm with a McIlwain chopper machine. The white part of the tissue was removed carefully with a tweezers before slicing. The slices were incubated in 5 ml buffer in the presence of 5 mM pargyline chloride. After incubation with 0.1 mM [³H]-5-HT for another 30 min the slices were transferred to a test tube and washed three times with the same volume of buffer. The slices were transferred to the superfusion chambers with a plastic pipette and were washed for 40 min. with the buffer in the presence of uptake inhibitor citalopram (2.5 µM) with a flow of 0.5 ml/min.

Electrical stimulation of 5-HT release

The superfused buffer was collected in 2 ml fractions. The slices were stimulated by electricity with a train of pulses of frequency 3 Hz, duration 2 ms and current 30 mA for 3 min at the 4th and 13th fractions. The tested drugs were added from the 8th fraction to the end of the experiment.

Results

A first electrical (or K^+) stimulation resulted in a standard amount of [3H] 5-HT released (S_1). Between the first and second stimulation the 5-HT_{1D} antagonist was added to the media which resulted in a dose depended increase of the release(S_2) after the second
5 stimulation. See Fig.1

The S_2/S_1 ratio which is the per cent of released [3H] 5-HT after the second stimulation (S_2) divided by that after the first stimulation (S_1), was used to estimate drug effects on transmitter release.

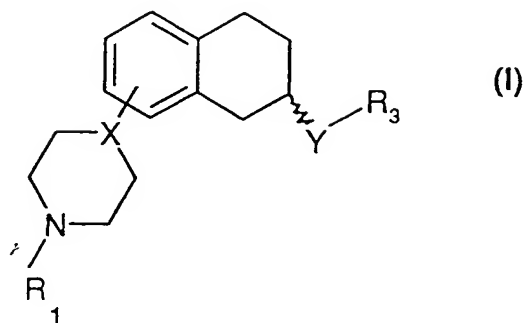
10

Compounds of the invention may also have the advantages that they may be less toxic, be longer acting, be more potent, have a broader range of activity, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

CLAIMS

1. A compound having the formula (I)

5



wherein

X is N or CH ;

10 Y is NR_2CH_2 , $\text{CH}_2\text{-NR}_2$, $\text{NR}_2\text{-CO}$, CO-NR_2 or NR_2SO_2 ;

R_1 is H, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl ;

R_2 is H or $\text{C}_1\text{-C}_6$ alkyl ;

R_3 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl or $(\text{CH}_2)_n\text{-aryl}$,

where aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted with R_4 and/or R_5 ;

15 R_4 is H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, halogen, CN, CF_3 , OH, $\text{C}_1\text{-C}_6$ alkoxy, NR_6R_7 , OCF_3 , SO_3CH_3 , SO_3CF_3 , $\text{SO}_2\text{NR}_6\text{R}_7$, phenyl, phenyl- $\text{C}_1\text{-C}_6$ alkyl, phenoxy, $\text{C}_1\text{-C}_6$ alkyl phenyl, $\text{C}_1\text{-C}_6$ alkyl-heterocyclic ring containing one or two heteroatoms or substituted heteroatoms selected from N, O, S, SO and SO_2 , an optionally substituted heterocyclic

20 heteroaromatic ring containing one or two heteroatoms or substituted heteroatoms selected from N, O, S, SO and SO_2 wherein the optionally substituent(s) may be selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl and phenyl- $\text{C}_1\text{-C}_6$ alkyl; or COR_8 ;

R_5 is H, OH, CF_3 , OCF_3 , halogen, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ alkoxy;

R_6 is H, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl;

25 R_7 is H, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl;

R₈ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, CF₃, NR₆R₇, phenyl, or a heterocyclic ring containing one or two heteroatoms or substituted heteroatoms selected from N, O, S, SO and SO₂;

n is 0-4;

as (R)-enantiomer, (S)-enantiomer or a racemate in the form of the free base or a

pharmaceutically acceptable salt or hydrate thereof.

2. A compound according to claim 1 in the form of (R)- enantiomer.

3. A compound according to any one of claims 1-2 wherein the piperidinyl or piperazinyl is in the 8 position.

4. A compound according to any one of claims 1-2 wherein the piperidinyl or piperazinyl is in the 5 position.

5. A compound according to any one of claims 1-4 wherein Y is NR₂CO and R₂ is H or CH₃.

6. A compound according to any one of claims 1-4 wherein Y is CONR₂ and R₂ is H or CH₃.

7. A compound according to any one of claims 1-6 wherein R₃ is (CH₂)_n-phenyl wherein phenyl is para-substituted with R₄ and n is 0.

8. A compound according to any one of claims 1-7 wherein R₄ is C₁-C₆ alkyl, phenyl, phenyl-C₁-C₆ alkyl, cyclohexyl, piperidino, morpholino, CF₃, 4-piperidon-1-yl, 1-pyrrolyl, C₁-C₆ alkoxy or COR₈ wherein R₈ is phenyl, cyclohexyl, piperidino, 1-piperazinyl, morpholino, CF₃ or 4-piperidon-1-yl.

9. A compound according to claim 1 wherein Y is NHCO, R₁ is H or C₁-C₆ alkyl, R₂ is H, R₃ is (CH₂)_n-phenyl wherein phenyl is para-substituted with R₄ and n is 0, where R₄ is piperidino, morpholino, thiomorpholino, 4-piperidon-1-yl or n-butoxy.

5 10. A compound which is

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(trifluoroacetyl)benzamide,

(*R*)-*N*-[8-(1-Methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,

10 (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-piperidinobenzamide,

(*S*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-*N,N*-diethylaminobenzamide,

(*R*)-*N*-[8-(4-Propylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-ethylbenzamide,

15 (*R*)-*N*-[8-(4-Methylpiperazine-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinocarbonylbenzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-butoxybenzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(1H-pyrrol-1-yl)benzamide,

20 (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-methyl-4-morpholinobenzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-ethylphenyl)benzamide,

25 (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylbenzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(*N,N*-dipropylaminosulphonyl)benzamide,

(*R*)-*N*-[8-(4-Ethylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,

(*R*)-*N*-[8-(1-Methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-trifluoromethylbenzamide,

(*R*)-*N*-[8-(1-Methylpiperidin-4-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-butoxybenzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-cyclohexylbenzamide,

5 (*R*)-*N*-[8-(Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-piperidon-1-yl)benzamide,

(*R*)-*N*-8-(Piperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide,

N-(4-Morpholinocarbonylphenyl)-8-[4-(methylpiperazin-1-yl)]-1,2,3,4-tetrahydronaphthalene-2-carboxamide,

10 (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-morpholinomethyl)benzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(*N,N*-dimethylaminocarbonyl)benzamide,

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-

15 morpholinocarbonylbenzamide or

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-thiomorpholinobenzamide,

in the form of a free base or pharmaceutical acceptable salt or hydrate thereof.

20 11. A compound which is

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-2-methylbenzamide

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-cyanobenzamide

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-fluorobenzamide

25 (*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-(4-hydroxyphenyl)benzamide

(*R*)-*N*-[8-(4-Methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-3-phenoxybenzamide

in the form of a free base or pharmaceutical acceptable salt or hydrate thereof.

12. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1-11 as an enantiomer or racemate in the form of a free base or a pharmaceutically acceptable salt or hydrate thereof optionally in association with diluents, excipients or inert carriers.

13. A pharmaceutical formulation according to claim 12 for use in the treatment of 5-hydroxytryptamine mediated disorders.

14. A pharmaceutical formulation according to claim 12 for use in the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders, pain, hypertension, urinary incontinence, vasospasm and growth control of tumors.

15. A compound as defined in any of claims 1-11 for use in therapy.

16. A compound as defined in any of claims 1-11 for use as a 5-HT_{1D} antagonist.

17. A compound as defined in any of claims 1-11 for use in the treatment of 5-hydroxytryptamine mediated disorders.

18. A compound as defined in claim 17 for use in the treatment of 5-hydroxytryptamine mediated disorders in the central nervous system.

19. A compound as defined in claim 18 for use in the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders, pain, hypertension.

20. A compound as defined in claim 17 for use in the treatment of 5-hydroxytryptamine mediated urinary incontinence, vasospasm and growth control of tumors.

5 21. The use of a compound defined in any of claims 1-11 in the manufacture of a medicament for the treatment of 5-hydroxytryptamine mediated disorders.

22. The use of a compound defined in any of claims 1-11 in the manufacture of a medicament for the treatment of 5-hydroxytryptamine mediated disorders in the central
10 nervous system.

23. The use of a compound defined in any of claims 1-11 in the manufacture of a medicament for the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco
15 abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders, pain, hypertension.

24. The use of a compound defined in any of claims 1-11 in the manufacture of a
20 medicament for the treatment of 5-hydroxytryptamine mediated urinary incontinence, vasospasm and growth control of tumors.

25. The use of a compound defined in any of claims 1-11 in the manufacture of a medicament acting as a 5-HT_{1D} antagonist.

25 26. A method for the treatment of 5-hydroxytryptamine mediated disorders by administering to a mammal including man in need of such a treatment a therapeutically effective amount of a compound defined in any of claims 1-11.

27. A method according to claim 26 for the treatment of 5-hydroxytryptamine mediated disorders in the central nervous system.

28. A method according to claim 27 wherein a 5-HT_{1D} antagonist is required for treatment.

5

29. A method according to claim 27 for the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders, pain, hypertension

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30. A method according to claim 27 for the treatment of 5-hydroxytryptamine mediated urinary incontinence, vasospasm and growth control of tumors.

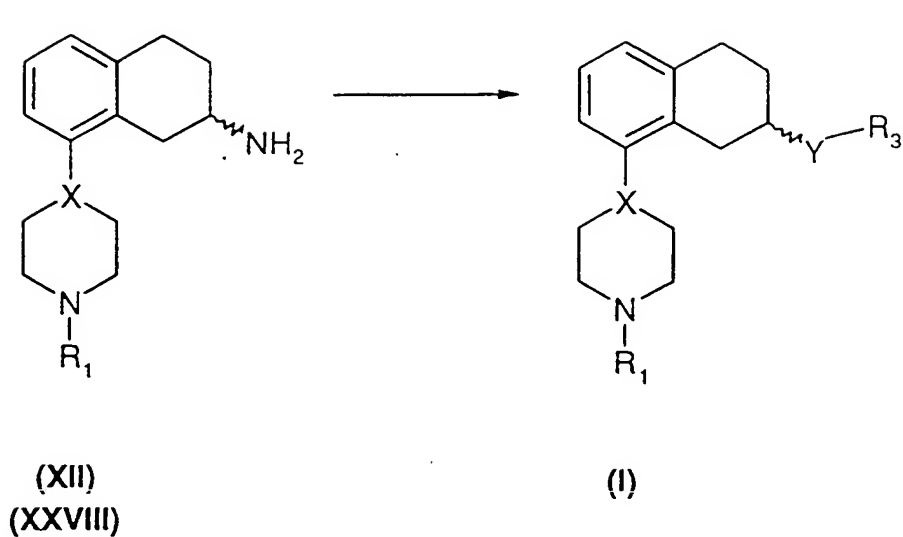
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31. A process for the preparation of the compound of formula (I) according to claim 1 by

A(i). acylation, in the case when R₁ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl, Y is NR₂CO, R₂ is hydrogen, X is N or CH and R₃ is as defined in general formula (I) in claim 1, of a compound of formula (XII) or (XXVIII)

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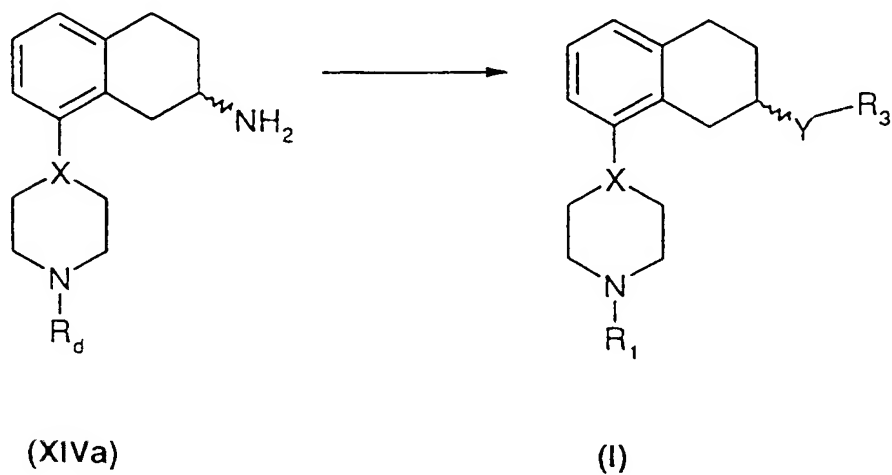
127



with an activated carboxylic acid $R_3\text{-COL}$ where L is a leaving group; or by using a carboxylic acid $R_3\text{-COOH}$ with an activating agent;

5

A(ii). acylation, in the case when R_1 is hydrogen, Y is NR_2CO , R_2 is hydrogen, X is N or CH and R_3 is as defined in general formula (I) in claim 1, of a compound of formula (XIVa) where R_d is a protecting group

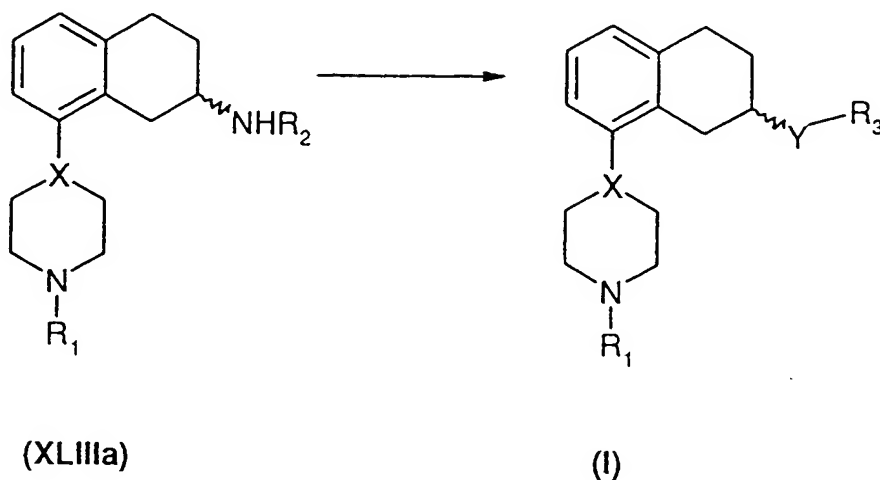


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with an activated carboxylic acid $R_3\text{-COL}$ where L is a leaving group, or by using a carboxylic acid $R_3\text{-COOH}$ with an activating agent followed by the removal of the protecting group R_d ;

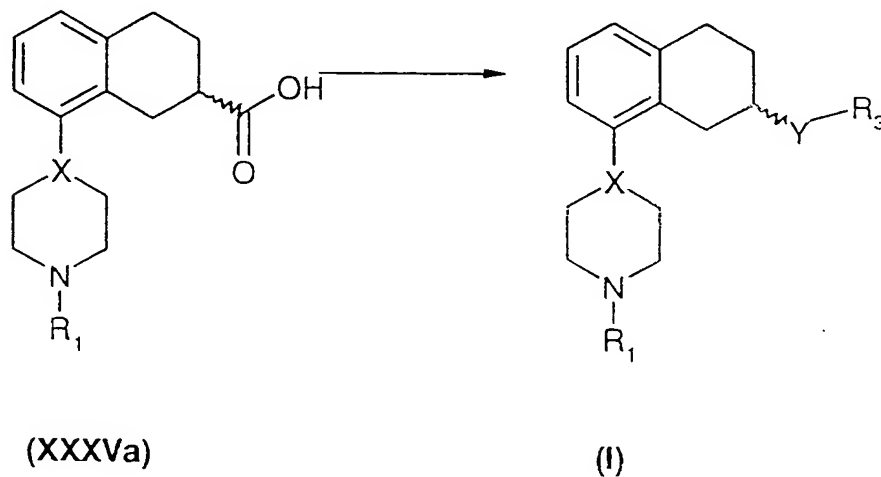
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A(iii). acylation, in the case when R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl, Y is NR_2CO , R_2 is C_1 - C_6 alkyl, X is N or CH and R_3 is as defined in general formula (I) in claim 1, of a compound of formula (XLIIIa)



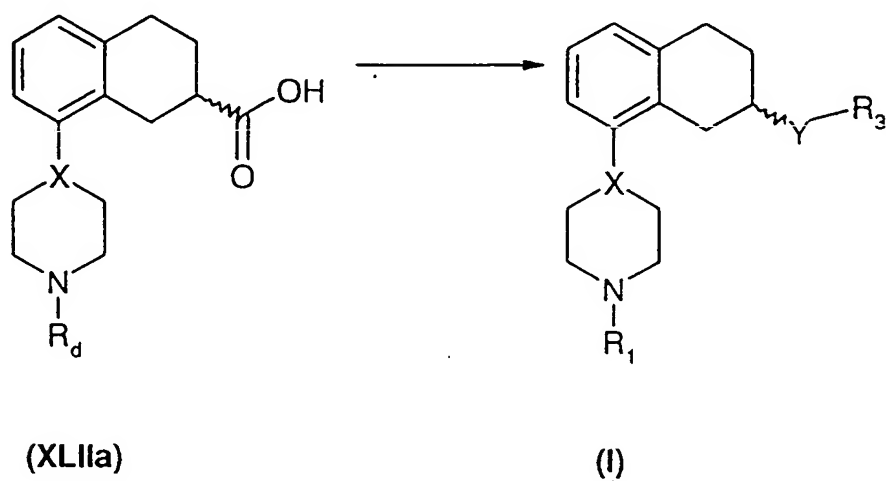
with an activated carboxylic acid R_3-COL where L is a leaving group, or by using a carboxylic acid R_3-COOH with an activating agent;

- 10 B(i). reacting, in the case when R_1 is C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl, Y is $CONR_2$, R_2 is hydrogen or C_1 - C_6 alkyl, X is N or CH and R_3 is as defined in general formula (I) in claim 1, an activated carboxylic acid of a compound of formula (XXXVa)



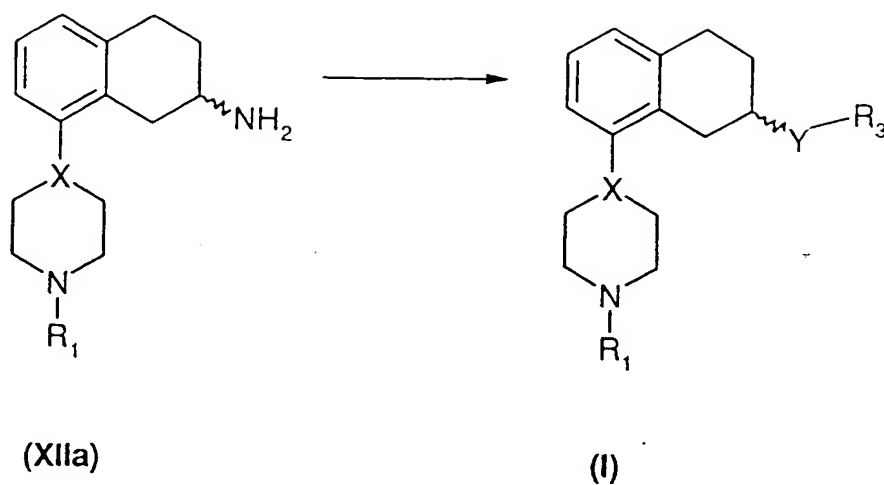
with an aniline or amine HNR_2R_3 ;

B(ii). reacting, in the case when R_1 is hydrogen, Y is CONR_2 , R_2 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl, X is N or CH , R_d is a protecting group and R_3 is as defined in general formula (I) in claim 1,
 5 an activated carboxylic acid of a compound of formula (XLIIa)



with an aniline or amine HNR_2R_3 , followed by removal of the protecting group R_d .

C. reacting, in the case when R_1 is $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl, Y is NR_2SO_2 , R_2 is hydrogen, X is N or CH and R_3 is as defined in general formula (I) in claim 1,
 10 a compound of formula (XIIa)



with an activated sulfonic acid $R_3\text{-SO}_2\text{L}$ where L is a leaving group;

5 D. reducing a compound of general formula (I) obtained from

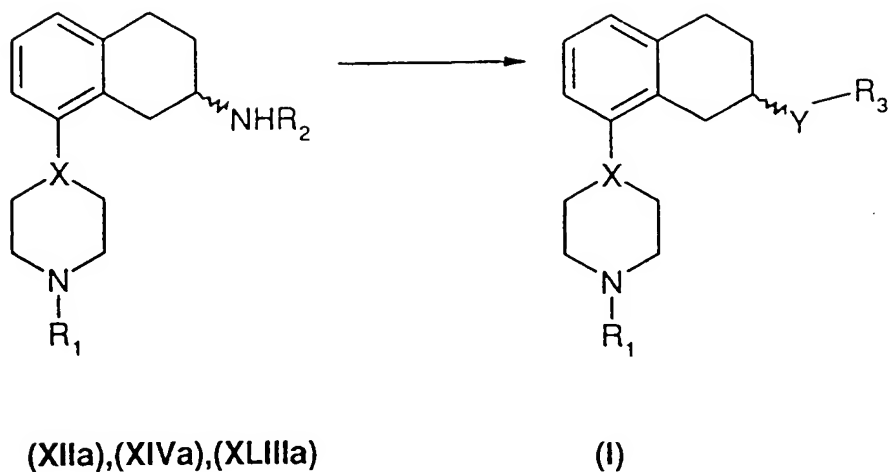
(i) methods A(i), A(ii) or A(iii) to a compound of general formula (I), where R_1 is hydrogen, $C_1\text{-C}_6$ alkyl or $C_3\text{-C}_6$ cycloalkyl, Y is NR_2CH_2 , R_2 is hydrogen or $C_1\text{-C}_6$ alkyl, X is N or CH and R_3 is as defined in general formula (I) in claim 1;

10

(ii) methods B(i) or B(ii) to a compound of general formula (I), where R_1 is hydrogen, $C_1\text{-C}_6$ alkyl or $C_3\text{-C}_6$ cycloalkyl, Y is CH_2NR_2 , R_2 is hydrogen or $C_1\text{-C}_6$ alkyl, X is N or CH and R_3 is as defined in general formula (I) in claim 1;

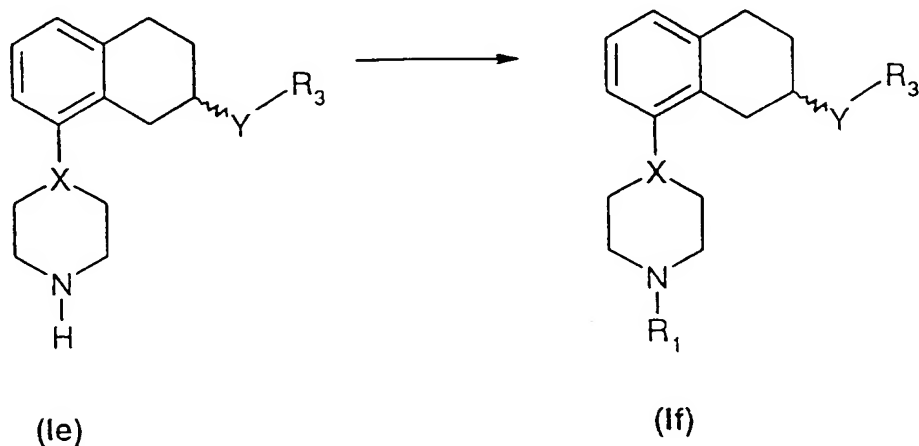
15 E. alkylation, in the case when R_1 is $C_1\text{-C}_6$ alkyl or $C_3\text{-C}_6$ cycloalkyl, Y is NR_2CH_2 , R_2 is hydrogen or $C_1\text{-C}_6$ alkyl, X is N or CH and R_3 is as defined in general formula (I) in claim 1, of a compound of formulae (XIIa), (XIVa) or (XLIIIa)

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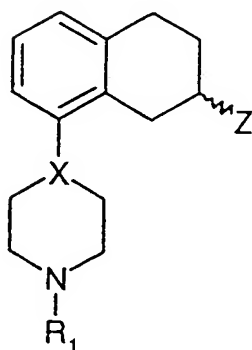
with a compound R_3CH_2-L where L is a leaving group such as a halogen e.g. bromine or chlorine or a alkyl- or arylsulfonyloxy group such as a mesylate or tosylate, and optionally followed by removal of protecting groups.

F. alkylation, in the case when R_1 is C_1-C_6 alkyl, Y is NR_2CO , R_2 is hydrogen or C_1-C_6 alkyl, X is N or CH and R_3 is as defined in general formula (I) in claim 1, of a compound of formula (Ie)



with a compound R_1-L where L is a leaving group such as a halogen e.g. bromine or chlorine or a alkyl- or arylsulfonyloxy group such as a mesylate or tosylate.

32. A compound having the formula



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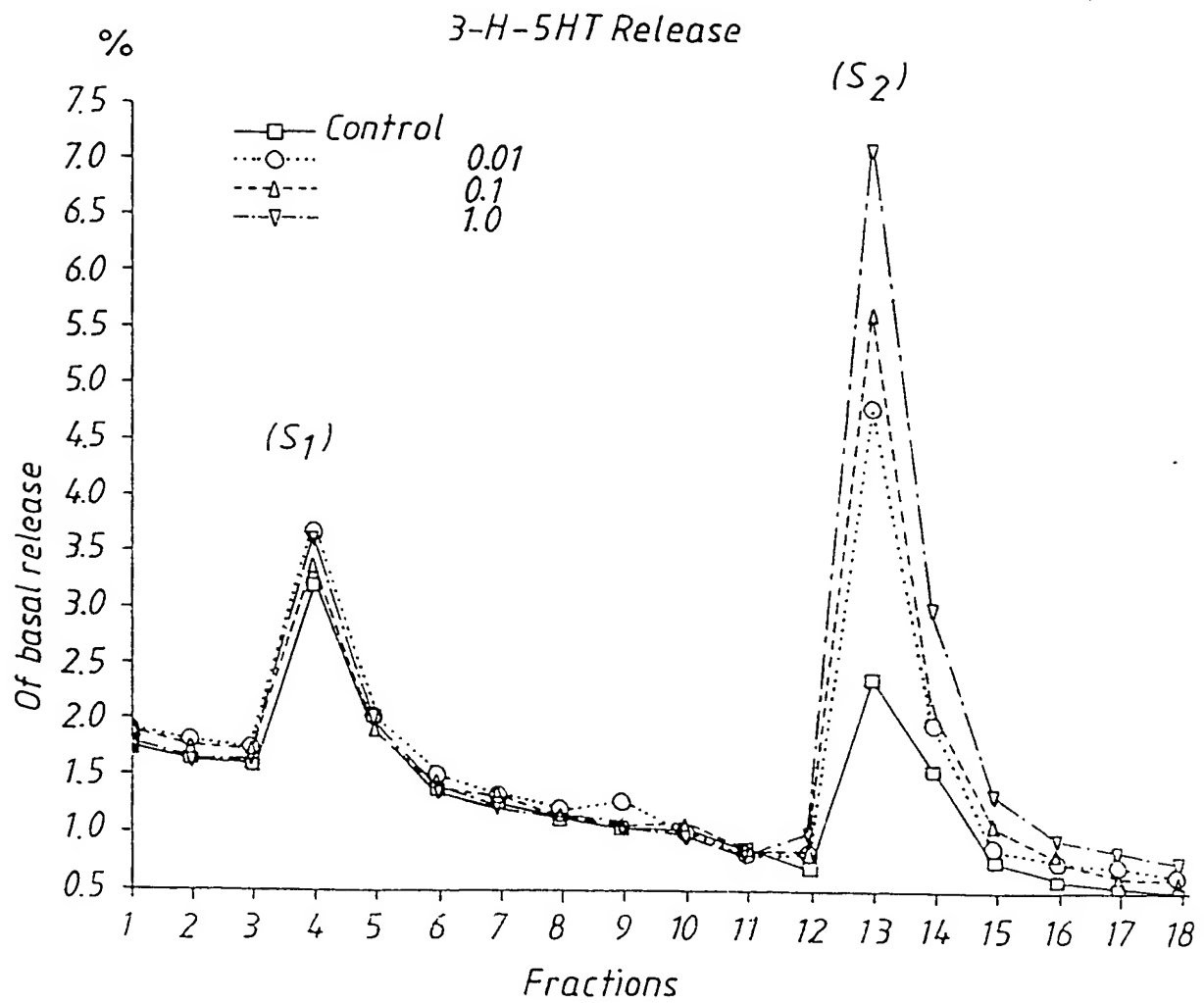
wherein Z is NH₂ or COOH;

X is CH or N; and

10 R₁ is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl.

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Fig. 1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/00469

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 295/135, C07D 295/155, C07D 211/26, C07D 211/34, A61K 31/495,
A61K 31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9421619 A1 (PFIZER INC.), 29 Sept 1994 (29.09.94), the claims; page 3,6-7,21-22 -- -----	1-32

☐

Further documents are listed in the continuation of Box C.

☒

See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

7 July 1997

Date of mailing of the international search report

12.07.97

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Swedish Patent Office
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/00469

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 26-30
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☒ Claims Nos.: 1
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The wordings "...or a heteroaromatic ring.." and "an optionally substituted heterocyclic or heteroaromatic ring" are too broadly formulated to permit a meaningful search. The search on claim 1 has therefore been incomplete.
(See Art 6).
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/07/97

International application No.

PCT/SE 97/00469

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9421619 A1	29/09/94	AU 6391894 A	11/10/94
		CA 2158457 A	29/09/94
		EP 0689536 A	03/01/96
		FI 941213 A	17/09/94
		HU 67312 A	28/03/95
		HU 9400760 D	00/00/00
		IL 108923 D	00/00/00
		JP 8503228 T	09/04/96
		ZA 9401806 A	15/09/95
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